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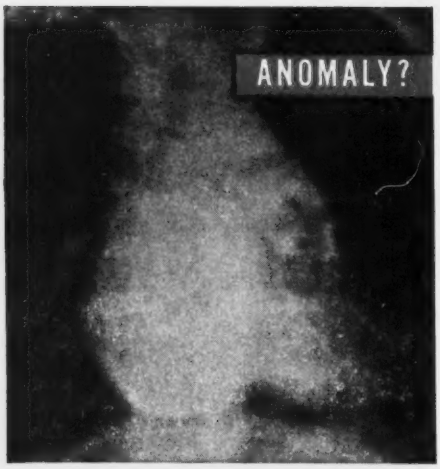

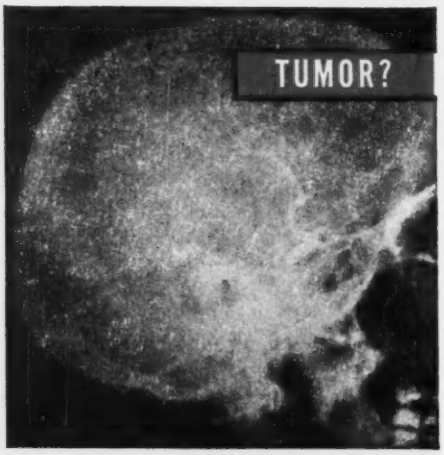

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Comparison of Indirect and Direct Methods of Measuring Arterial Blood Pressure

By FREDERICK H. VAN BERGEN, M.D., D. STUART WEATHERHEAD, M.D., ALAN E. TRELOAR, PH.D., ALLAN B. DOBKIN, M.D., AND JOSEPH J. BUCKLEY, M.D.

Direct and indirect determinations of blood pressure have been recorded in 70 human subjects. Statistical analysis of the results is presented. A frequent discrepancy between direct and indirect readings is evident with the drift of the latter falling increasingly below the direct measurement as blood pressure rises. The greatest discrepancy is found in the young hypertensive subject and the possible clinical implications of this finding are discussed. An attempt is made to explain some of the factors contributing to the variable error by which auscultatory readings underestimate the true intraarterial pressure.

IN the course of recording arterial pressures of patients subjected to hypotensive anesthesia, it was observed that blood pressures often were unobtainable by any of the indirect methods, while at the same time intra-arterial manometry demonstrated systolic levels of 60 to 70 mm. Hg. One frequently is impressed by the uncertainty, if not inadequacy, of blood pressure determinations upon patients in surgical shock when indirect methods alone are employed.

Clinicians, using the three indirect methods under customary conditions, have observed disturbing discrepancies among the results obtained. The usual practice of employing one technic only does not permit such revelations. False confidence in absolute values thus arises all too easily.

Conflicting opinions exist concerning the validity of auscultatory pressures.[1] Several observers[2-4] in studies of the inaccuracy of indirect determinations have enumerated factors contributing to the errors. Others[5-8] report good agreement between blood pressures determined by the direct intra-arterial and the auscultatory methods.

Cognizant of the confusion existing in this basic physiologic measurement, we undertook the following investigation to compile data seeking to define the relative accuracy of the three indirect methods over a wide blood pressure range, and to identify some of the factors contributing to the current enigma.

METHODS

Indirect Measurement of Blood Pressure. Two to four trained observers participated sequentially in determining auscultatory systolic and diastolic levels, and oscillometric and palpatory systolic levels, on each patient, using a mercury manometer. Care was taken to insure that these observers did not see the intra-arterial pressure recordings. Another assistant entered each observer's indirect blood pressure findings on the tracings at the appropriate points.

In the determination of auscultatory systolic and diastolic pressure, the standards recommended by Bordley and his co-workers[8] were followed. Oscillometric systolic pressure was recorded as the point on the manometer scale at which the meniscus of the pulsating mercury column became convex. Palpatory systolic pressures were determined by the perception of a pulse in the radial artery. Diastolic

From the Division of Anesthesiology, and the Division of Biostatistics, University of Minnesota, Minneapolis, Minn.

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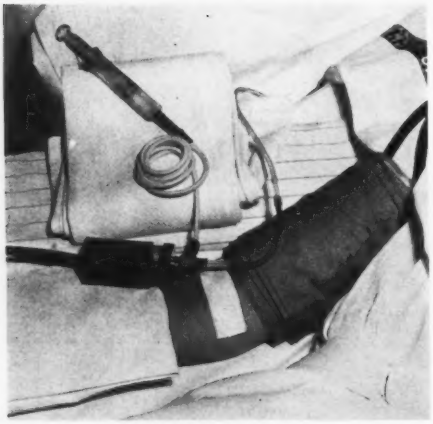

FIG. 1. Strain gage-needle system employed in recording brachial artery pressures. Stopcock connects system to pressure bottle for square wave production and to a syringe containing 2.5 per cent sodium citrate for "flushing out" the system.

levels were not recorded by either the oscillometric or the palpatory methods.

Direct Measurement of Blood Pressure. The intra-arterial pressure was measured directly with high accuracy by means of a standard resistance wire pressure transducer (model P23A Statham strain gage) and registered by a direct-writing electronic recorder (Sanborn Polyviso). A 15 gage needle, connected directly to the face of the transducer by a double male adapter, was inserted into the brachial artery directly under the lower edge of the blood pressure cuff (fig. 1). This entire system was demonstrated to have a 100 per cent frequency response, flat to 17.5 cycles per second. There was a 105 per cent response at 23 cycles per second (fig. 2).

The system was calibrated statically against a mercury manometer before and after each recording. Square waves of 200 mm. Hg were passed before, during, and after each recording to detect damping due to clotting or malposition of the needle.

Reading the Tracings. The Sanborn Polyviso has a recording accuracy of ±0.5 mm. deflection within the inner 4 cm. of the recording paper. This increases an additional ±0.5 mm. deflection error in the remaining 0.5 cm. at each margin of the paper. With the attenuation used to cover the pressure ranges involved, the over-all reading accuracy was judged to be within ranges of ±2.5 mm. Hg in the center 4 cm. of the paper and within ±5 mm. Hg in the marginal 0.5 cm.

In quantifying the tracings an average of the individual systolic and diastolic levels for a period of 15 seconds immediately before beginning inflation of the cuff was used. This was deemed desirable so that effects of variations in blood pressure produced by respiration, irregular cardiac rhythm and such other minor factors might be minimized. Tracings immediately following deflation of the cuff were not used.

SUBJECTS

The subjects in the present study consisted of 70 surgery patients ranging in age from 2.5 to 82 years (average of 52 years). In every instance the blood pressure comparisons were made in the immediate postoperative period while the subjects still were partially under the effects of general anesthesia. All measurements were made with the patients in a horizontal supine position.

The subjects used for these observations and the conditions prevailing were not normal. It may be inferred safely from the average age (52 years) that many of the patients were either mild or severe hypertensives. Many of the patients were afflicted with some form of cardiovascular disease other than hypertension. The postoperative and postanesthetic states are often accompanied by marked alterations in stroke volume output, blood volume, total peripheral resistance, pulse pressure and heart rate. Nevertheless, these subjects and these conditions represent a cross section of the surgical patients who require careful and accurate monitoring of their blood pressures during the operative and postoperative periods.

RESULTS

Circumstances delimited both the period of observation and number of available observers for these blood pressure determinations on each patient. With 5 of the 70 subjects,

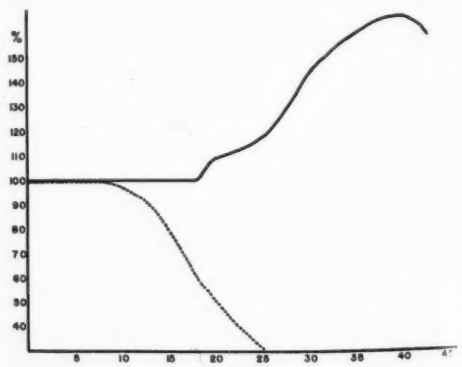

FIG. 2. Graph illustrating the frequency response curves of the two recording systems employed in this study. Solid line represents the strain gage–15 gage needle system; broken line represents the strain gage–catheter system. Ordinate line in per cent response. Abscissae line in cycles per second.

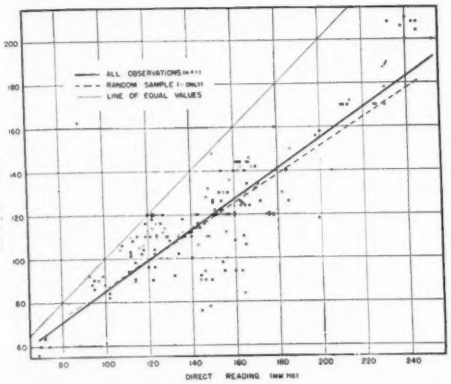

FIG. 3. Relationship of auscultatory reading to direct determination of systolic blood pressure.

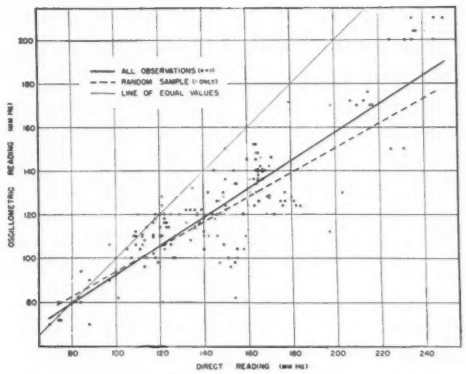

FIG. 4. Relationship of oscillometric reading to direct determination of systolic blood pressure.

only one direct reading was secured, followed immediately by one each of the indirect measurements in four cases and only the auscultatory measurements in the other. For the remaining 65 subjects, 2 to 14 direct measurements were made, with varying numbers of indirect determinations.

In studying the relationship between the direct measurement and each of the indirect determinations of blood pressure, we have available 180 values for auscultatory systolic pressure, 133 auscultatory diastolic, 166 oscillometric systolic, and 132 palpatory systolic. Each indirect reading has its associated direct reading taken closely if not immediately in advance of it. Thus there are from 132 to 180 pairs of values defining the relationships, each of the 70 subjects contributing from 1 to 7 points for the 3 correlation surfaces.

The possibility of disturbing effects arising from the unequal representation of the 70 subjects led us to select one pair of values at random from each subject for each of these three associations, using a table of random numbers. Thus we established a sample of paired values for each association in which there was no possibility of disturbance arising from considering patients unequally.

The basic data need not be reproduced here in tabular form. Graphic methods will be adequate. Figures 3, 4 and 5 present the correlation scatters for the three relationships of indirect determination of blood pressure to the direct method of measurement. Each solid dot or open circle defines a pair of associated values for some patient; the corresponding direct and indirect blood pressure values may be ascertained by tracing these points to the horizontal and vertical scales, respectively.

The inscribed thicker straight lines define the *average* relationship of the indirect reading of blood pressure to the direct measure. Since the latter has negligible error in comparison with the indirect determination, it is appropriate to consider only this line for the average relationship when errors alone reduce the correlation below perfection. The full line is fitted to all available pairs of values (dots plus circles). The broken line is fitted only to the

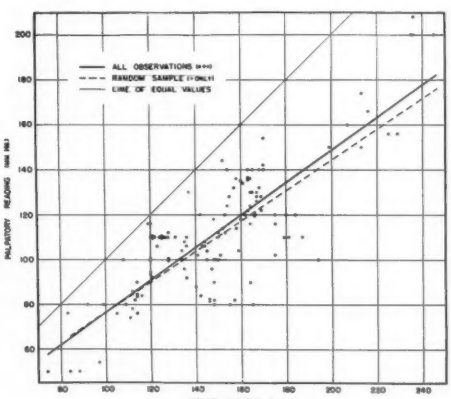

FIG. 5. Relationship of palpatory reading to direct determination of systolic blood pressure.

random sample of 1 point per patient (defined by the circles). These heavy lines are the statistical regression lines. The light diagonal line is that of equal values on the two scales; the distribution of the point scatter in relation to this line defines the nature of the errors of the indirect method relative to the direct method over the range of values covered.

Certain features common to all three relationships are outstanding. First, over the entire range of observations, indirect readings of blood pressure fall below the direct measurement made as nearly as possible at the same time. There was only one case of equality in 611 paired observations, and relatively few approaches to equality. Second, the drift of indirect readings is to fall increasingly below the direct measurement as blood pressure increases. Third, no serious disturbance is introduced by considering *all* values (as opposed to one per patient for the random sample) in arriving at these average relationships. We therefore have chosen to use the total sample lines in further discussion.

The three regressions of indirect on direct readings (using all observations) are superimposed in figure 6. It will be observed that the oscillometric method makes the nearest approach on the average to equality with the direct reading. The palpatory method falls furthest from the equality line in these data, with auscultatory results holding the intermediate position. It would be unwise to conclude that these rather small divergences of

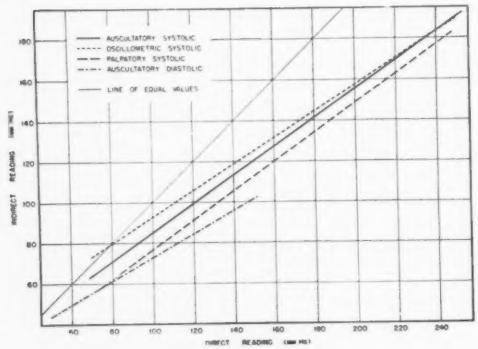

FIG. 6. Regressions of indirect readings on direct determination of blood pressure.

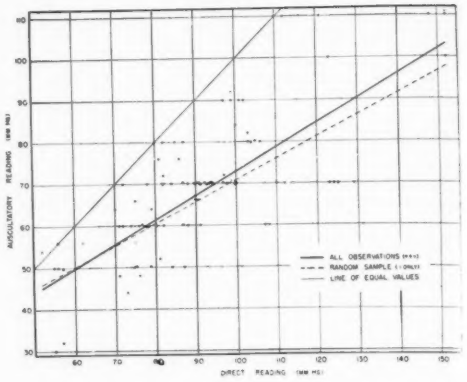

FIG. 7. Relationship of auscultatory reading to direct determination of diastolic blood pressure.

the three regressions among themselves would persist if more extensive data were available. However, there would be no question about their departure in general (collectively) from the equality line.

Figure 6 also includes the regression of auscultatory diastolic reading. The full scatter of points, together with the regression and equivalence lines for the auscultatory diastolic data, is given in figure 7. It is interesting to note that the agreement of indirect and direct readings is even less satisfactory for diastolic pressures than for systolic pressures. The *absolute* errors of the indirect readings on the average are of the same general order of magnitude as for the auscultatory systolic pressure at each end of the line. Since the general level of diastolic pressures is much less than for systolic pressures, the errors become much more important in the relative sense.

It is of some interest to consider at this point the inter-relationships of the indirect readings, one to the other, for systolic pressure. The charts are reproduced as figures 8, 9 and 10. Since both variables are now subject to error, and one may presume more or less equally so, there is less justification for considering only one of the two regression lines which may be drawn for each surface. However, the amount of data available to us for this study is limited to not more than 47 points. We shall omit, therefore, regression analysis and be content to study the scatters alone.

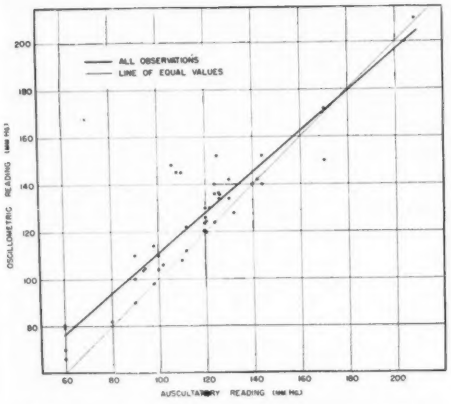

FIG. 8. Correlation between auscultatory and oscillometric readings of systolic blood pressure.

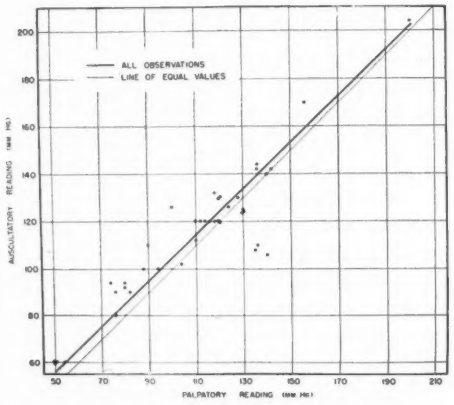

FIG. 9. Correlation between auscultatory and palpatory readings of systolic blood pressure.

It will be noted that there is comparatively good agreement between these indirect readings. As before, the thin diagonal line traces equal values by both methods. It will also be noted that the scatters of points are in closer agreement with this line than in figures 3, 4 and 5. This would be anticipated from the proximity of the regression lines in figure 6. Because of the restricted number of paired values we would not care to suggest that indications of somewhat closer agreement in one pair than another are suitable bases for claims that such better agreement does exist in general. However, it is noticeable that these readings agree with one another as individual pairs more

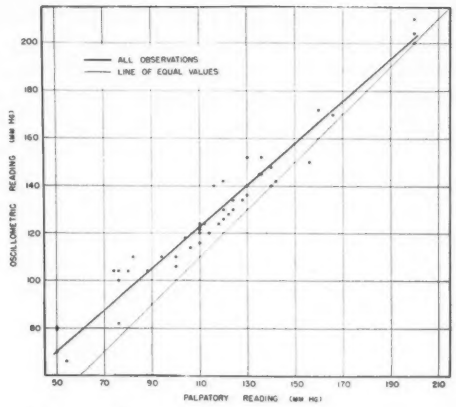

FIG. 10. Correlation between oscillometric and palpatory readings of systolic blood pressure.

closely, in general, than each indirect reading agrees with its direct associate. That is, the intensity of correlation in figures 8, 9 and 10 is greater than in figures 3, 4, and 5. This may arise from circumstances; the direct reading is unknown to an observer, whereas his indirect readings cannot very well be dismissed from mind immediately as each is made.

The Relationship of Body Build, Age and Pulse Pressure to Auscultatory–Direct Blood Pressure Measurement

1. Body Build. The patients were divided into three weight groups (48 slim, 88 medium and 39 heavy) to study whether there is any

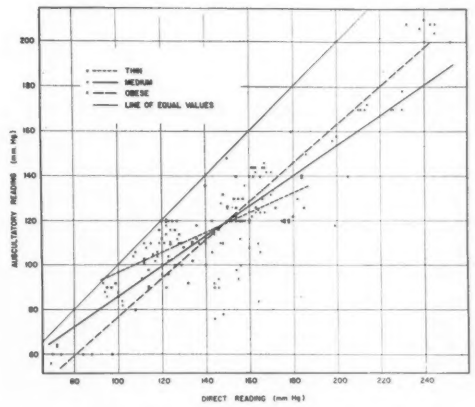

FIG. 11. Weight as a factor in the correlation of indirect and direct systolic blood pressure readings.

influence of body build on the accuracy of systolic auscultatory determinations. Figure 11 presents the full scatters and regressions of auscultatory pressure on direct pressure for the three weight groups.

It is interesting to note that the three regressions form a systematic array of lines intersecting at essentially the same value of approximately 150 mm. Hg direct systolic pressure. Variation in blood pressure is very wide for both the heavy and medium build patients, and relatively restricted only for the thin persons. But the average divergence of auscultatory reading from direct determination is more variable for the thin than for the heavy, ranging from 0 to 45 mm. Hg for the former and 20 to 40 mm. Hg for the latter.

2. Age. The results of regrouping to study this relationship are given in figure 12. Since weight tends to increase with age, it is not surprising that there is some similarity between figures 11 and 12. Unfortunately our data are too scant to allow of age analysis within weight groups.

It is evident that the two older age groups could well be combined to present a sharper contrast with the younger group. Since the regression line of the young age group slopes rapidly away from the line of equivalence, one is challenged by the implication that serious errors exist in determining auscultatory pressures of young hypertensive patients.

3. Pulse Pressure. Auscultatory systolic

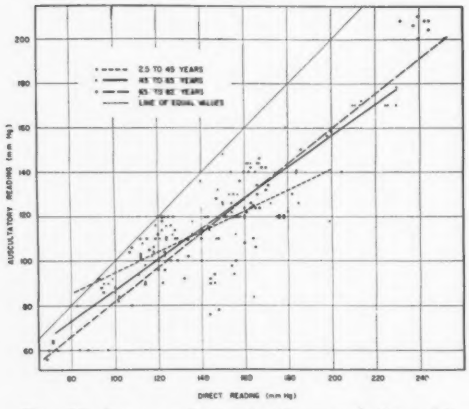

FIG. 12. Age as a factor in the correlation of indirect and direct systolic blood pressure readings.

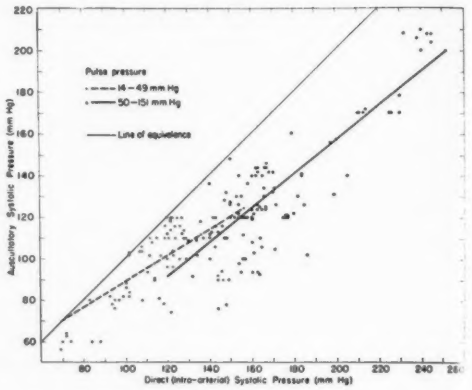
Pulse pressure
16 – 49 mm Hg
50 – 151 mm Hg
Line of equivalence
Auscultatory Systolic Pressure (mm Hg)
Direct (intra-arterial) Systolic Pressure (mm Hg)

FIG. 13. Effect of pulse pressure on the auscultatory regression lines (all samples).

pressure regression lines were computed to determine the influence of pulse pressure upon their slope (fig. 13). For this purpose the data were divided into two groups on the basis of the direct intra-arterial pulse pressures; the first group consisted of 76 observations in which the pulse pressures ranged from 14 to 49 mm. Hg, while the second consisted of 104 observations where the pulse pressure ranged from 50 to 151 mm. Hg.

The regression line of the low pulse pressure group slopes away from the line of equivalence more rapidly than the line of the high pulse pressure group. The suggestion is that, on the average, errors in auscultatory systolic readings are different for persons of low pulse pressure than for those with high pulse pressure.

DISCUSSION

Accuracy of the Direct Recording System. Attention should be drawn to the importance of the fluid filled system used to conduct dynamic pressure changes to the diaphragm of the transducer. The frequency response characteristics of both the transducer and the recorder have been shown to be more than adequate for recording pressure pulse waves.[9] The limiting factor of all such systems, then, is the needle or catheter and its connections to the pressure transducer. This is particularly true where accurate reproduction of the detailed components of a pressure pulse wave

ire desired. Even in this instance expert observers do not agree on the *over-all frequency response* required. Wood[9] reports no significant differences in recorded pressure levels when measured by different manometer systems with uniform response out to 6 cycles per second and above.

In this particular study we have been concerned with the systolic and diastolic levels rather than the actual configuration of the pressure pulse waves. The system was underdamped at the higher frequencies since it produced a 100 per cent response flat to 17.5 cycles per second followed by overshoot as the frequency increased. To determine the accuracy of this recording system, a comparative test was carried out. A second recording system which produced a 100 per cent response flat to only 7.5 cycles per second (fig. 2) was arranged by using a 22.5 cm. length of small bore (*0.5* mm. inside diameter) polyvinyl catheter. This catheter was threaded into the brachial artery through an 18 gage needle. A 15 gage needle was inserted beside it. The orifices of both catheter and needle were at the same level within the artery. Simultaneous recordings were made and analyzed. Figure 14 illustrates the findings. No appreciable difference exists in the pressure levels recorded by the two systems. The only noticeable alteration produced by the catheter was a phase lag of 0.03 second.

A second factor which conceivably could account for differences in direct and indirect pressure measurements was considered. The indirect methods determine the lateral pressure against the wall of the artery, whereas the direct method used here determined the end-on thrust of pressure against the diaphragm of the transducer. In the latter instance higher readings might result from the additive effect of kinetic energy imparted to the stagnant fluid column of the recording system. To determine the error introduced by measuring an end-on systolic pressure, a second comparative experiment was carried out. A simultaneous recording of end-on and end-away pressures was obtained by introducing two 15 gage needles in opposite directions into the brachial artery. The results are shown in figure 15. It will be

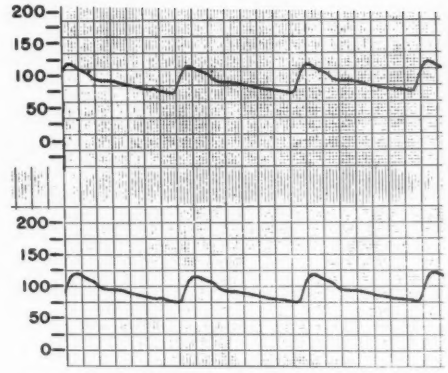

FIG. 14. Simultaneous records of pressure pulses from the brachial artery as recorded with a 15 gage needle (*upper*) and a fine bore polyvinyl catheter (*lower*). Note that the base line of the upper tracing is shifted upward.

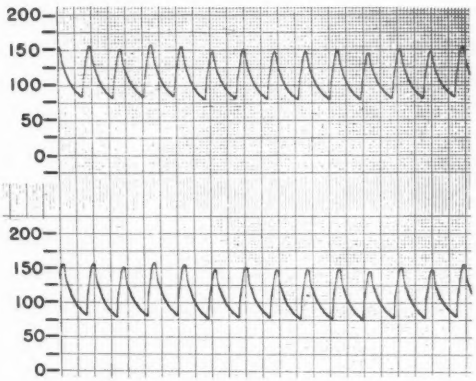

FIG. 15. Simultaneous tracings of brachial pressure pulses as recorded with a 15 gage needle directed centrally (*upper*) and a 15 gage needle directed peripherally (*lower*).

noted that no appreciable difference exists between these two recordings.

Oscillometric Method. In observing oscillometric systolic pressures it is conceivable that the values obtained may be higher than the intra-arterial pressures. This may be explained by the pulsating column of blood proximal to the inflated cuff striking its upper edge and producing an oscillation of the mercury column. This condition was most apt to occur when measuring the systolic pressure of children with a small sized cuff.

Auscultatory Method. Contrary to the find-

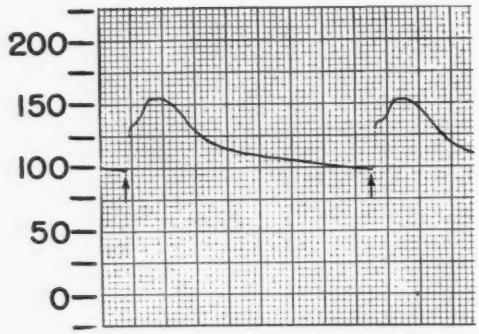

FIG. 16. Pressure pulse waves recorded during cuff pressure of 130 mm. Hg. The arrows indicate the negative dip which precedes the anacrotic rise when Korotkoff sounds are present.

ings of others[3] the indirect auscultatory and palpatory systolic observations never exceeded the simultaneous direct pressure readings in our observations.

Although the mechanisms effecting the Korotkoff sounds are not wholly understood, the conclusions of Erlanger[10] concerning a preanacrotic phenomenon seem tenable. He found that at a compression pressure just below the proximal endarterial pressure a small increment of blood is forced through the flattened segment of artery. This blood is insufficient in amount to distend the compressed segment and the segment remains flattened until the compression pressure is reduced further. The pulse then succeeds in penetrating the entire length of the segment and a *diastolic residuum* results. Not until this diastolic residuum is formed is it possible for the preanacrotic phenomenon (fig. 16) to occur with its concomitant sounds of Korotkoff.

In one phase of our study endarterial and auscultatory readings were recorded simultaneously from the same arm and distal to a compression cuff (fig. 17). The procedure was as follows. The cuff was inflated rapidly to a level well above the endarterial systolic pressure, maintained there for several seconds and then slowly deflated. Prior to deflation the endarterial pressure level fell toward the equilibrium pressure of 20 mm. Hg. During deflation of the cuff a slow rise in the level of the direct tracing developed, followed by the appearance of small pressure waves. Shortly thereafter, sounds of Korotkoff could be obtained. It was noted that the initial slow rise in the endarterial pressure level occurred at a compression pressure approximately equal to the previously determined endarterial systolic pressure. Some workers[3, 6] have published similar tracings wherein it was demonstrated that the first small pressure waves distal to the compressing cuff could be synchronous with the first auscultatory sound.

We assume from these studies that these small pressure waves represent increments of blood penetrating the artery under the cuff during systole at a compression pressure which completely flattens the compressed segment during diastole. When the compressing pressure becomes low enough for the endarterial pressure to maintain a diastolic residuum, the preanacrotic phenomenon develops. And if this residuum develops with the first pulse wave to penetrate the cuff, the auscultatory and direct readings can be equal.

We are thus led to believe that, using the proper size of cuff and slow deflation, the

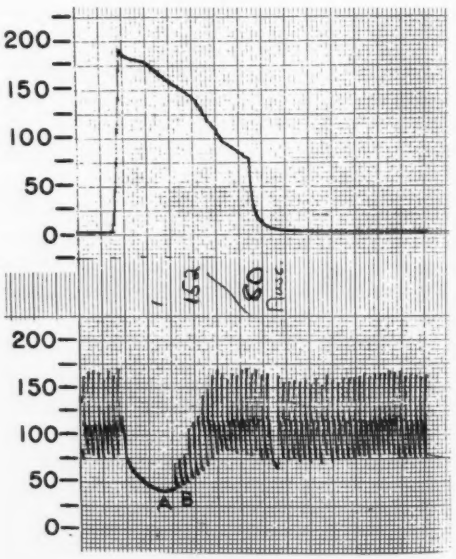

FIG. 17. Simultaneous records of changes in the brachial artery pressure (*lower*) related to the compression cuff pressure (*upper*). *A*, intra-arterial pressure rise beginning at compression pressure of 165 mm. Hg. *B*, first auscultatory sound heard at compression pressure of 152 mm. Hg.

auscultatory method for measurement of systolic blood pressure can be of varying degrees less than (or equal to) the true direct systolic pressure reading, but can never exceed this direct reading.

Roberts and associates[1] suggest that, as an index of diastolic pressure, the muffling of Korotkoff sounds is more accurate than the disappearance of the sounds. The frequency with which our diastolic readings grossly underestimate the intra-arterial pressure seems to support this view. We recorded levels according to the disappearance of sounds as recommended by Bordley and his colleagues.[8]

Wave Summation. According to Wiggers[11] a centripetal rebound wave of pressure summates upon the primary centrifugal systolic wave resulting in the peak systolic level. That the magnitude of the summation wave is a function of peripheral resistance has been demonstrated in a circulation model.[11]

Direct tracings were recorded in which the peripheral resistance was increased by occlusion of the brachial artery distal to the needle (fig. 18). Invariably this increase in peripheral resistance resulted in an elevation of the direct systolic pressure of 20 to 30 mm. Hg. It is of interest to note that the values of auscultatory systolic pressures did not vary under the two conditions. From this observation one might assume that the difference between direct systolic and auscultatory systolic pressures could be the result of failure of the auscultatory method to register the *summation waves*. In turn this might mean that the appearance of the first sound of Korotkoff depends primarily upon the pressure of the centrifugal wave. If this is true, then the auscultatory systolic level is most likely an index of the central aortic pressure rather than the peripheral pressure in the vessel at the site of measurement. In the light of the foregoing assumptions an increase in general peripheral resistance is primarily registered by direct recording methods, whereas the indirect auscultatory observations are affected only secondarily by the increased work load on the heart resulting in an increased systolic pressure thrust.

Such a relationship might account for some

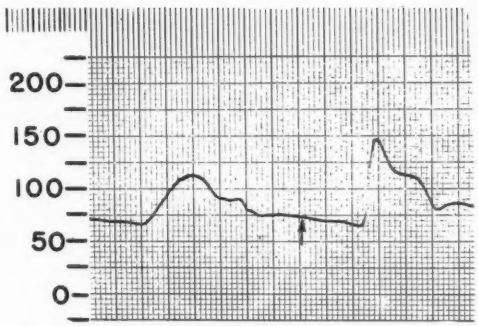

FIG. 18. Pressure pulse waves from the brachial artery. The arrow indicates the point at which the artery was occluded by digital compression distal to the point of recording.

of the discrepancies between direct and auscultatory readings encountered in this study. We make particular reference to our findings in the young hypertensive patients. In this group, usually, the arteriolar bed maintains a high degree of tonus. It seems reasonable to assume that such a state would augment the summation effect of the reflected wave upon the central wave resulting in a peripheral intra-arterial pressure higher than that obtained with the auscultatory method.

The findings in the young hypertensive group pose some interesting possibilities. If the auscultatory method is frequently in error in a young patient with moderate systolic elevation, an intra-arterial measurement may well be an indicated procedure in the investigation of such an individual. Early detection of some cases destined to develop a severe hypertension syndrome may be facilitated. It is also possible that information gained from such direct measurements might be of value in estimating the degree of hypertension, as a guide in the evaluation of therapy and in the formulation of a prognosis.

CONCLUSIONS

1. Direct and indirect determinations of blood pressure are compared in 70 patients in the immediate postoperative state, and the results of statistical analysis of these data are presented.

2. These studies demonstrate a frequent discrepancy between the direct and indirect readings.

3. The greatest discrepancy is found in the young hypertensive group. The possible clinical value of this finding is considered.

4. The decreasing order of accuracy for indirect methods of measurement is shown to be: oscillometric, auscultatory and palpatory.

5. The drift of indirect readings is to fall increasingly below the direct measurement as blood pressure rises.

6. The usual practice of employing one indirect technic only is not subject to criticism if the observer regards such a pressure estimation as an index to the true intra-arterial pressure. Changes in blood pressure can be detected by such a method but no conclusion should be drawn concerning absolute values.

7. An attempt is made to explain some of the factors contributing to the variable error by which auscultatory readings underestimate the true intra-arterial pressure.

Sumario Español

1. Determinaciones de presión arterial directas e indirectas son comparadas en 70 pacientes en el estado postoperatorio inmediato, y los resultados de un análisis estadístico de estos datos se presentan.

2. Estos estudios demuestran una frecuente discrepancia entre las lecturas directas e indirectas.

3. La mayor discrepancia se encuentra en el grupo hipertenso joven. El posible valor clínico de este hallazgo se considera.

4. El orden descendente de precisión para los métodos indirectos de medir la presión ha mostrado ser; oscilométrico, auscultatorio y palpatorio.

5. El rumbo de las lecturas indirectas es el de caer progresivamente por debajo de las lecturas directas a medida que la presión arterial aumenta.

6. La práctica usual de emplear una técnica indirecta solamente no esta sujeta a la crítica si el observador considera tal estimado de la presión como un índice de la presión intra-arterial verdadera. Cambios en presión arterial se pueden determinar por este método pero una conclusión sobre los valores absolutos no se debe aceptar.

7. Un atentado se hace para explicar algunos de los factores contribuyentes al error variable por el cual lecturas auscultatorias indirectas resultan más bajas que la presión verdadera intra-arterial.

Acknowledgment

The authors are indebted to Miss Nancy Thiel, R.N., and Miss Marilyn Johnson, R.N., for their painstaking assistance in recording of indirect blood pressures, and to Loren R. Sheldahl, B.A., Research Assistant in the Division of Biostatistics, for his compilation and statistical analysis of the data.

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Observations Concerning the Production and Excretion of Cholesterol in Mammals

XIV. The Relationship of the Hepatic Reticuloendothelial Cell (Kupffer Cell) to Endogenously Produced Cholesterol

By MEYER FRIEDMAN, M.D., AND SANFORD O. BYERS, PH.D.

WITH THE TECHNICAL ASSISTANCE OF BARBARA GUNNING, B.S., CLARENCE OMOTO, B.S., AND WARREN HAYASHI, B.A.

The possible role of the hepatic reticuloendothelial system in the synthesis as well as the disposition of endogenously produced cholesterol was studied in the rat by various means. Our results suggest that this system does not synthesize significant quantities of cholesterol nor participate in the egress of endogenously produced cholesterol from the plasma into the liver. It does however, play an important, perhaps indispensable, role in ridding blood of cholesterol derived from the diet.

PREVIOUS morphologic, chemical and physiologic studies done in this laboratory[1, 2] indicate that the hepatic reticuloendothelial system of various mammals plays an essential role in the disposition of cholesterol derived from the intestine. Moreover, if the function of this system is experimentally interfered with by injection of various colloidal "blocking" agents, an accumulation not only of cholesterol but also of lipid and chylomicra occurs in the plasma of the treated animal.

Preliminary evidence obtained in the above studies, however, strongly suggested that the reticuloendothelial cells of the liver did not participate in the disposition of *endogenously* derived cholesterol. It was thought important then to investigate this point in more complete detail. The results of such a study presented herein confirm the initial observations in that they indicate that the hepatic reticuloendothelial cell does not appear to participate either in the synthesis of cholesterol or in the later disposition of that increment of cholesterol synthesized by the animal itself.

From the Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif.

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I. The Role of the Hepatic Reticuloendothelial System in the Synthesis of Cholesterol

Previous studies from this laboratory[3, 4, 5] have demonstrated that the liver of the animal maintained upon a cholesterol-free diet is constantly discharging into and later removing cholesterol from the plasma and, accordingly, at any given time the cholesterol content of the plasma is dependent chiefly, if not solely, upon the functional integrity of this organ. In other words, for all practical purposes the chief site of cholesterol synthesis from a quantitative standpoint is in the liver. Subsequent studies[6] demonstrated that an estimate of the rate of this hepatic function could be obtained by a determination of the daily biliary cholesterol excretion. A second indirect estimate of this function also could be obtained by measurement of the plasma cholesterol increase occurring after the intravenous administration of Triton because this latter substance when given in sufficient amount

causes the accumulation in the plasma of an animal, of all or almost all cholesterol manufactured and previously discharged by the liver.[7] The possible effect then of partial interference with the function of the hepatic reticuloendothelial cells by India ink injection upon the rate of the hepatic synthesis of cholesterol was studied by employing these two different methods of assay.

Methods

The bile ducts of 21 rats were cannulated and the bile subsequently collected for 24 hours was analyzed for its total cholesterol content. Eleven of these animals had received 0.5 ml. of 20 per cent India ink intravenously twice daily for 48 hours immediately prior to the duct cannulation.

A second series of 10 starved rats was given 100 mg. of Triton WR 1339 intravenously daily for 48 hours. Half of these rats also received India ink injections as described above. Plasma samples obtained before and 48 hours after the beginning of injections were analyzed for total cholesterol.

Results

The results obtained in the two different types of experiments indicated that any possible interference effected in hepatic reticuloendothelial cells by the injection of India ink had no effect upon the apparent rate of endogenous cholesterol synthesis as gauged by these two different methods.

The average cholesterol content of the 24-hour bile collection of the 11 rats injected with India ink was 1.7 mg. (range, 0.8–2.5), with a standard error of the mean of ±0.14, and the biliary cholesterol content of the 10 control rats was 1.8 mg. (range, 1.4–2.2) with a standard error of the mean of ±0.09.

The average plasma cholesterol of the five rats given Triton and ink rose from 65 to 637 mg. per 100 ml. (range, 509–704) in 48 hours, and in the control animals it rose from 65 to 620 mg. per 100 ml. (range, 589–653).

II. Morphologic Study of the Possible Role of the Hepatic Reticuloendothelial System in the Disposition of Endogenously Derived Cholesterol

Methods

A series of 10 young male rats (average weight, 245 Gm.) of the Long-Evans strain was given intravenously 20 mg. of cholesterol in the form of hypercholesteremic serum. This serum was obtained from rats which had been subjected to biliary obstruction 72 hours before and then given 200 mg. of cholate per day plus a sterol-free diet.[7] Prior to its injection, the serum was centrifuged at 18,000 revolutions per minute to remove any possible chylomicra.[8] Six of the 10 rats were sacrificed at six hours and four at 24 hours, after each had been injected one hour previously with 0.5 ml. of 20 per cent India ink solution. This latter injection was done in order to identify reticuloendothelial cells in the liver. A portion of the liver was fixed in 10 per cent formalin for 24 hours and frozen sections were made. One section of the liver was stained with Sudan III. A second section of each organ was heated for one hour at 55 C. and then examined with the polarizing microscope. For control purposes, six rats (average weight, 252 Gm.) were given orally 100 mg. of cholesterol dissolved in 3 ml. of Tween and three of the rats were sacrificed at six, and the remainder at 24 hours. Portions of their liver were treated and examined in similar fashion. The livers of three rats starved for 24 hours also were obtained and similarly fixed, stained and examined.

Results

The liver of the starved rats showed no sudanophilic granules (see fig. 1) either in the reticuloendothelial or the hepatic parenchymal cells. Neither were any doubly refractile bodies observed.

The liver of the rats given *endogenously* derived cholesterol by intravenous injection exhibited at the end of six hours a moderate amount of sudanophilic granules which were contained almost exclusively within the parenchymal cells (see fig. 2). Little or none was found between the parenchymal cells or in the reticuloendothelial cells. However the liver of the rats given *oral* cholesterol six hours previously, exhibited sudanophilic granules which were almost exclusively *between* the parenchymal cells (see figs. 3*a* and 3*b*) and either in or about the reticuloendothelial cells. Examination of liver sections under polarized light revealed the deposit of refractile bodies *within* the hepatic parenchymal cells of the rats which had received the endogenously derived cholesterol and their aggregation either in or about the hepatic reticuloendothelial cells of the rats which had received *oral* cholesterol.

A similar selective localization within the

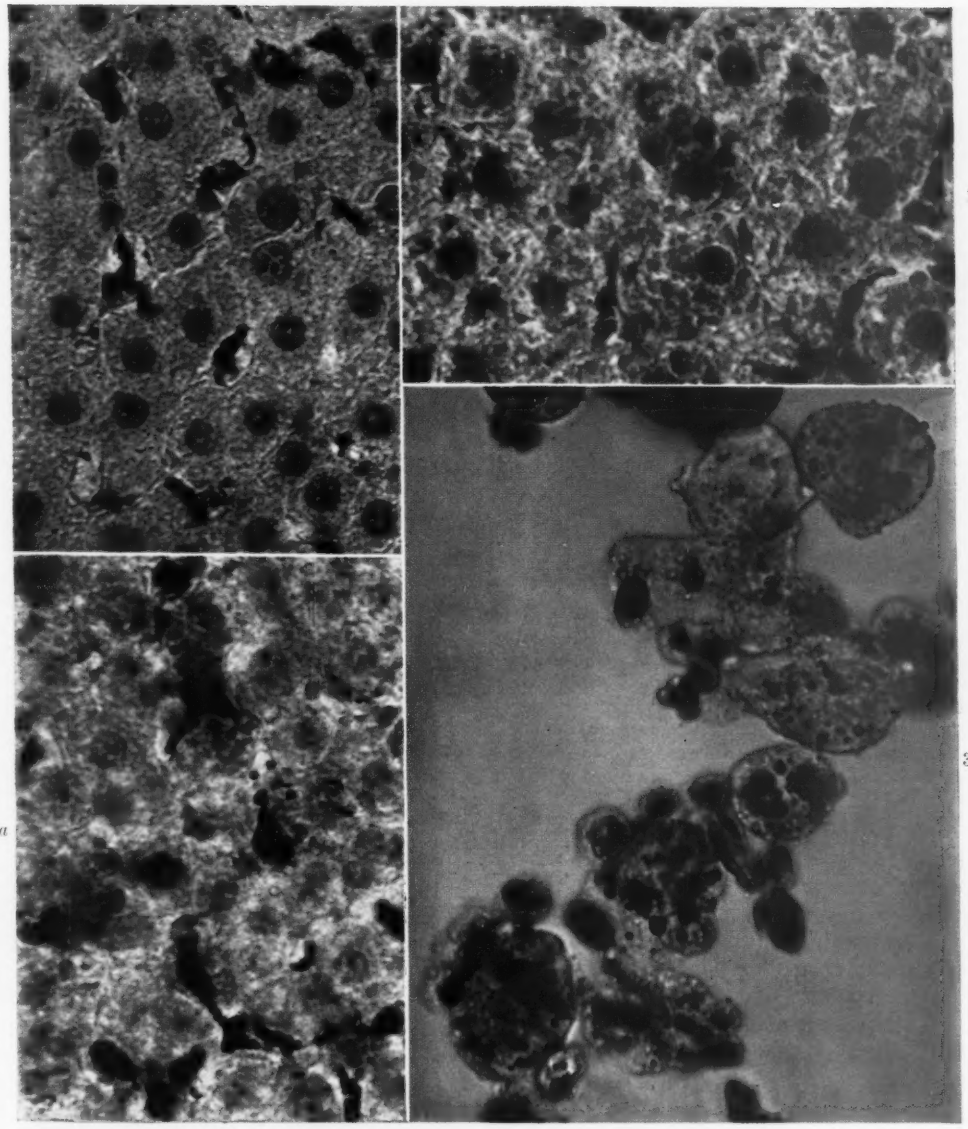

FIG. 1. Liver of starved rat. The reticuloendothelial cells are identified by the ink particles contained in them. Note the absence of stainable lipid. (Sudan III and H. & E. ×600.)

FIG. 2. Liver of starved rat, six hours after the intravenous injection of 20 mg. of cholesterol in form of hypercholesteremic serum. Note lipid bodies (red) within the hepatic parenchymal cells with none in or about the reticuloendothelial cells. (Sudan III and H. & E. ×600.)

FIG. 3. (*a*) Liver of rat six hours after oral ingestion of 100 mg. of cholesterol. Note lipid accumulation in and about ink-containing reticuloendothelial cells. Little or none is observed in parenchymal cells at this time. (Sudan III and H. & E. ×600.) (*b*) Isolated, ink-containing reticuloendothelial cells obtained from liver of rat fed 100 mg. of cholesterol 24 hours previously. Note the lipid granules within the cytoplasm of these cells. (Sudan III ×800.)

(The use of color in figures 1, 2 and 3 is made possible by a grant from Winthrop-Stearns, Inc., to the publication fund of the American Heart Association.)

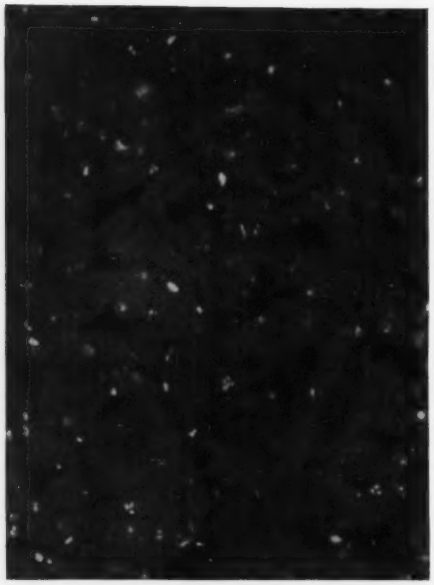

FIG. 4. Liver of rat, 24 hours after intravenous injection of 20 mg. of cholesterol in form of hypercholesteremic serum. Observe the refractile bodies (cholesterol) distributed entirely in the parenchymal cells and away from the ink-containing reticuloendothelial cells. The photograph represents a double exposed film. The first exposure was to ordinary light and the second to polarized light. (Unstained ×400.)

parenchymal cell also was found to occur (see fig. 4) in the liver of rats, 24 hours after the intravenous injection of cholesterol. Conversely, in the rats given oral cholesterol 24 hours previously, the greatest deposition of cholesterol still appeared in and about the reticuloendothelial cells (see fig. 5), although at this time, a considerable amount of cholesterol also appeared to be present in the parenchymal cells.

III. Effect of Intermittent Injection of India Ink upon the Hepatic Deposition of Endogenously Derived Cholesterol

The preceding observations strongly suggested that the reticuloendothelial cells participated only in the disposition of exogenously derived cholesterol and that these cells were "bypassed" by endogenously derived cholesterol when injected in soluble, chylomicron-free serum. If this were so, then interference with reticuloendothelial cell function by injection of India ink should not impede the rate of hepatic deposition of this type of cholesterol. The following experiment therefore was carried out to determine this point.

Methods

Ten young male rats (average weight, 230 Gm.) were given intravenously, 20 mg. of endogenously derived cholesterol (in the form of hypercholesteremic serum) per day for 48 hours. Half of these rats also were injected intravenously twice daily with 0.5 ml. of 20 per cent India ink suspension. At the end of 48 hours, a portion of the liver was removed, fixed and stained as described above. For control purposes, eight rats (average weight, 246 Gm.) were given 100 mg. of cholesterol dissolved in 3 ml. of olive oil daily for 48 hours. Five of these control rats also received similar injections of India ink. Portions of the liver were treated and examined as described above.

Results

The injection of India ink was not found to influence the apparent rate of cholesterol

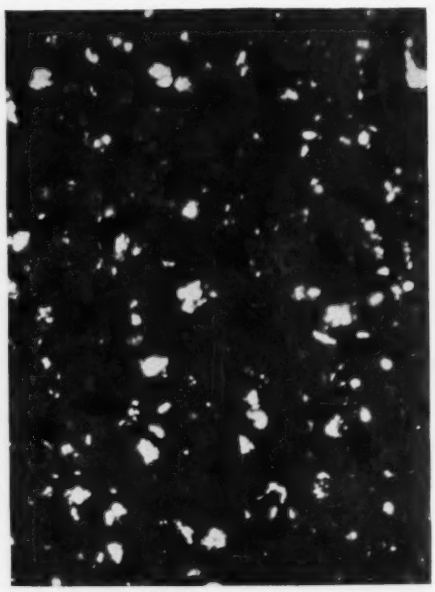

FIG. 5. Liver of rat, 24 hours after oral ingestion of 100 mg. of cholesterol. Note the abundance of refractile bodies and the close proximity of many to the ink containing reticuloendothelial cells as compared with figure 4. The photograph was obtained exactly as described in legend of figure 4. (×400.)

deposit in the rats which had been injected with endogenously derived cholesterol. Thus the liver of the rats injected with India ink exhibited as intense sudanophilic staining as the liver of the rats which had received no ink. The density of the refractile bodies also appeared (see and compare figs. 6 and 7) to be about the same in the two groups of rats.

On the other hand, the liver of rats which were given oral cholesterol and also ink exhibited a profound reduction in sudanophilic staining as compared with the liver of rats given oral cholesterol alone. This same difference also was observed in the comparative density of refractile bodies in the liver of the two groups (see and compare figs. 8 and 9).

These results suggested that "blocking" of hepatic reticuloendothelial cells interfered with the hepatic deposition of dietary but not endogenously derived cholesterol; a finding indirectly confirming the previous morphologic ones concerning the differences in the cellular mode of entrance of the two differently derived cholesterol moieties.

FIG. 6. Liver of rat, 48 hours after the daily intravenous injection of 20 mg. of endogenously derived cholesterol for 48 hours. Note the distribution of refractile bodies is chiefly within parenchymal cells. The photograph is also a doubly exposed one. (×400.)

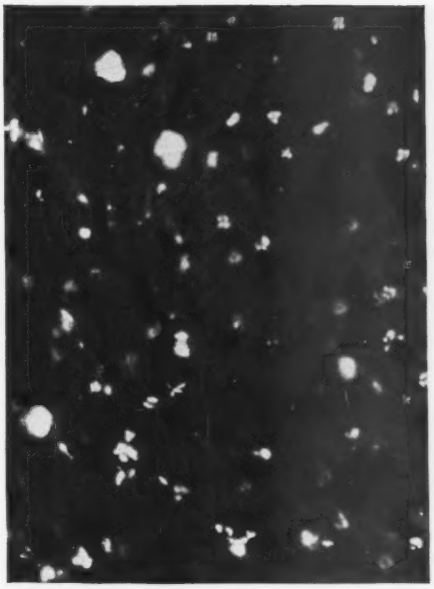

FIG. 7. Liver of a rat treated exactly as that whose liver is shown in figure 6 except that it was also given 0.5 ml. of 20 per cent India ink twice daily. Note that the quantity and distribution of the refractile bodies is almost identical with that shown in figure 6. Photograph obtained as described in figure 6. (×400.)

IV. Effect of Injection of India Ink upon the Plasma Cholesterol of Rats Given Excess Cholesterol of Endogenous Origin by Parenteral Injection

The above demonstrated inability of injected India ink to prevent or retard the hepatic deposition of endogenously derived cholesterol strongly suggested that the hypercholesteremia observed in animals receiving India ink and *exogenously* derived cholesterol in our previous studies[1, 2] would not occur if endogenously derived cholesterol were substituted. Experiments therefore were done to determine this point.

Methods

A series of 21 normal, male, Long-Evans rats (average age, 15 weeks) were given intravenously 25 mg. of cholesterol daily for 48 hours in the form of hypercholesteremic serum obtained and rendered chylomicron free as described in section II. This quantity of cholesterol was given parenterally as this is the approximate amount which was found[9] to be

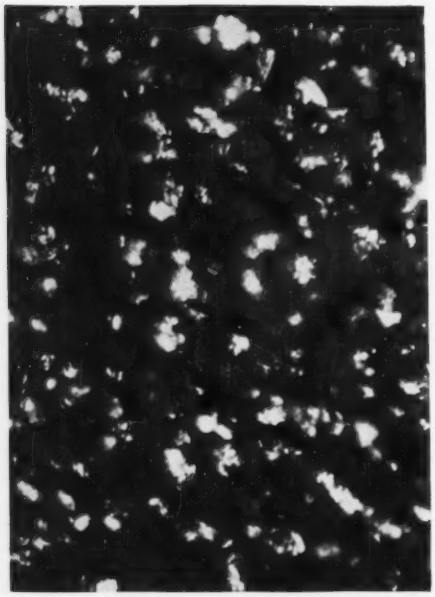

FIG. 8. Liver of a rat given 100 mg. of cholesterol daily for 48 hours. As compared to livers shown in figures 6 and 7, there are many more refractile bodies present in this liver, and many are in close approximation to the ink containing reticuloendothelial cells. Photograph obtained as described in figure 6. (×400.)

absorbed from the intestinal tract of rats given 100 mg. of cholesterol by mouth. Twelve of these rats also received intravenously 0.5 ml. of 20 per cent India ink suspension twice daily for 48 hours.

A second control series of 22 rats of the same strain and age received 100 mg. of cholesterol dissolved in 3 ml. of olive oil orally each day for 48 hours. Twelve of these rats also received India ink as described above.

Plasma samples obtained before, and 48 hours after the beginning of the experiment were analyzed for total cholesterol and examined grossly for degree of turbidity and microscopically for chylomicra.

Results

As table 1 demonstrates, the rats of series I which only received 25 mg. of endogenously derived cholesterol daily by intravenous injection failed to exhibit hypercholesteremia. Similarly, those rats receiving India ink together with their injections of endogenous cholesterol also failed to exhibit hypercholesteremia, turbidity or chylomicronemia.

On the other hand, whereas the control rats of series II which received only 100 mg. of oral cholesterol did not exhibit hypercholesteremia (see table 1), turbidity or chylomicronemia, the other rats of series II which had received India ink injections with their oral feeding of cholesterol exhibited hypercholesteremia, a moderate turbidity, and intense chylomicronemia.

These results indicated that rats injected with India ink failed to become hypercholesteremic when given endogenously derived cholesterol despite the fact that they were given parenterally the same amount of cholesterol known to be absorbed in rats fed oral cholesterol and which became hypercholesteremic.

V. Effect of Injection of India Ink upon the Plasma Cholesterol of Rats Given Excess Cholesterol of Mixed Origin by Parenteral Injection

The preceding observations strongly suggested that although two series of animals

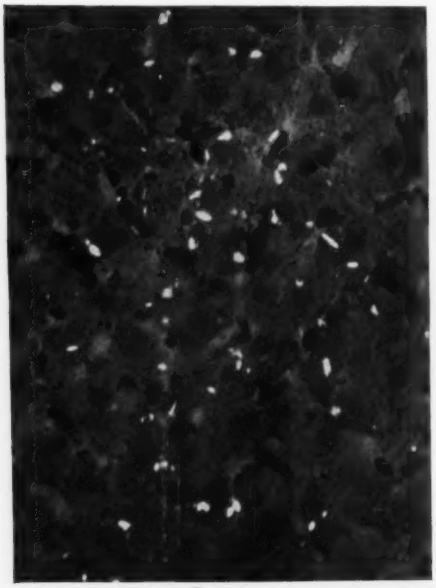

FIG. 9. Liver of a rat treated exactly as that whose liver is shown in figure 8 except that it was given 0.5 ml. of 20 per cent India ink twice daily. Observe the marked absence of refractile bodies in this liver as compared to their abundance in the liver shown in figure 8. Photograph obtained as described in figure 6. (× 400.)

TABLE 1.—*The Effect of Intravenous Injection of India Ink upon the Plasma Cholesterol of Rats also Given (I) Intravenous Cholesterol of Endogenous Origin and (II) Oral Cholesterol*

Average Plasma Cholesterol (mg./100 ml.)

No. of Rats	Av. Wt. (Gm.)	Before Injection	48 Hours after Injection	Plasma Turbidity (48 hours)	Chylomicronemia (48 hours)
I. *Rats Given Intravenous Cholesterol of Endogenous Origin (25 mg./Day)*					
A. *With Injections of India Ink*					
12	295	48	55	Absent	Absent
Range	(252–414)	(38–50)	(35–76)		
S.E.Mean		±5.2	±4.1		
B. *Without India Ink Controls*					
9	281	49	68	Absent	Absent
Range	(250–340)	(37–53)	(50–78)		
S.E.Mean		±4.8	±3.6		
II. *Rats Given Oral Cholesterol (100 mg./Day)*					
A. *With Injections of India Ink*					
12	268	49	100	Present	Present
Range	(244–340)	(37–58)	(83–114)		
S.E.Mean		±4.2	±3.1		
B. *Without India Ink Controls*					
10	256	55	68	Absent	Absent
Range	(212–306)	(33–79)	(50–88)		
S.E.Mean		±4.8	±3.3		

received eventually the same quantity of cholesterol in their blood per day, "blocking" of the reticuloendothelial cells with India ink led to hypercholesteremia only in those rats which were fed cholesterol. One possible explanation for the observed hypercholesteremia in the latter rats might be that orally derived cholesterol is first discharged into the blood enmeshed as an insoluble increment of a chylomicron,[10] and that India ink competes with this latter particle for reticuloendothelial cell ingestion and in so doing leads to the observed chylomicronemia and a consequent hypercholesterolemia. On the other hand, those rats given endogenously derived cholesterol receive it directly into their blood stream as *soluble* cholesterol[10] and not entangled in lipid rich chylomicra. Accordingly, the latter type of cholesterol may not need to be ingested by a process of phagocytosis, hence may not be capable of being interfered with in its transit from plasma to hepatic parenchymal cell by India ink injection. In order to investigate this possibility, the following experiments were done.

Methods

Pooled hypercholesteremic serum was obtained from hypercholesteremic rabbits which had been placed upon a high cholesterol diet two months previously. A portion of the pooled serum was centrifuged at 18,000 revolutions per minute for 30 minutes. At this speed, the chylomicra were forced into an upper, very creamy layer occupying no more than 10 per cent of the total volume. This upper layer was removed and discarded, and the lower layer was checked routinely before its use for the absence of chylomicra by microscopic examination under darkfield illumination. This type of centrifuged separation was carried out four times. The average cholesterol content of the four different *unchanged* sera was 1525 mg. per 100 ml. (range, 1120–1940), and that of the lower layer component of these same sera after centrifugation was 1195 mg. per 100 ml. (range, 885–1570).

Two series of normal male rats (average age, 14 weeks) of Long-Evans strain were anesthetized with

ether and operated upon, and an external lumbar vein was cannulated with polyethylene tubing connected to an apparatus delivering approximately 0.3 ml. of fluid per hour. This procedure has been described (in detail) in a previous study.[11]

The 21 rats of the first series received, by continuous intravenous injection, cholesterol in the form of the *unchanged* rabbit dietary hypercholesteremic serum sufficiently diluted with normal saline solution so that each rat received approximately 35 mg. of cholesterol a day for 48 hours. In addition, 12 of the rats received intravenously 0.5 ml. of 20 per cent India ink suspension twice daily for 48 hours. Plasma samples obtained before and 48 hours after the beginning of the injection were analyzed for total cholesterol content.

The 22 rats of the second series also received 35 mg. of cholesterol daily for 48 hours except it was given in the form of the lower layer of *centrifuged* rabbit dietary hypercholesteremic serum. Twelve of the rats also were injected with India ink as described above.

Results

As table 2 indicates, rats given 35 mg. of cholesterol per day in the form of *unchanged* rabbit dietary hypercholesteremic serum and also injected with ink exhibited a greater degree of hypercholesteremia at 48 hours than the control rats which received the same amount of cholesterol but no ink. Thus the average plasma cholesterol of the 16 ink-injected rats rose from 55 to 158 mg. per 100 ml. (see table 2), whereas that of the uninjected rats rose from 51 to 103 mg. per 100 ml. The difference moreover between the means of both series at 48 hours was found to be significant since on calculation it was found to be 3.2 times the standard error of the difference between the two means.

On the other hand, rats of the second series given the same quantity of cholesterol and in the same type of serum, except that the latter was cleared of chylomicra, exhibited no greater hypercholesteremia when injected with India ink than the controls. Thus the average plasma cholesterol of the eight ink-injected rats rose from 59 to 121 mg. per 100 ml. in 48 hours (see table 2) whereas that of the controls rose from 62 to 107 mg. per 100 ml. Calculation of the standard error of the difference between the two means at 48 hours indicated that it was approximately identical with the actual difference of the means con-

TABLE 2.—*The Effect of Intravenous Injection of India Ink upon the Plasma Cholesterol of Rats Given (A) Unchanged and (B) Centrifuged Rabbit Dietary Hypercholesteremic Serum.*

No. of Rats	Av. Wt.	Plasma Cholesterol (mg./100 ml.) Before Injection	Plasma Cholesterol (mg./100 ml.) 48 Hours after Injection
A. Injection of Unchanged Rabbit Dietary Hypercholesteremic Serum			
(1) Rats Given India Ink Injection			
16	257	55	158
Range	(212–304)	(33–78)	(100–321)
S. E.Mean		±9.6	±14.3
(2) Control Rats			
14	249	51	103
Range	(205–306)	(31–65)	(55–182)
S. E.Mean		±8.8	±9.5
B. Injection of Centrifuged Rabbit Dietary Hypercholesteremic Serum (Lower Layer)			
(1) Rats Given India Ink Injection			
8	231	59	121
Range	(200–278)	(42–75)	(91–165)
S. E.Mean		±4.4	±11.0
(2) Control Rats			
8	221	62	107
Range	(200–258)	(46–79)	(70–158)
S. E.Mean		±4.1	±7.9

noting that there was actually a good agreement between the two means.

These results suggested that when cholesterol was given in a serum containing a portion of its cholesterol as an insoluble increment of chylomicra,[10] "blocking" of hepatic reticuloendothelial cells interfered with the egress of such cholesterol from the plasma.

VI. The Possible Effect of Injection of India Ink upon the Function of the Mast Cells

Although the preceding experiments strongly suggested that injection of India ink affected hypercholesteremia only in animals supplied with exogenously derived cholesterol by partially preventing the ingestion of the latter by the hepatic reticuloendothelial cells, a possibility existed that perhaps the heparin discharge of the mast cells[12] was interfered

with. Such interference conceivably could reduce the circulating heparin increment necessary for the "clearing process" by which a turbid, chylomicron-rich plasma is rendered translucent and in the process has its cholesterol solubilized.

In order to determine this possibility, three of six rats were injected twice daily with 0.5 ml. of 20 per cent India ink suspension for 48 hours, at which time all of the rats were sacrificed and sections of various tissues (heart, liver, spleen, kidney, jejunum and skin) were fixed and stained for their mast cell contents both with toluidine blue and thionine blue.[12] The number and condition of the mast cells of the various tissues of the ink-injected rats appeared to be exactly similar to those of the uninjected rats. No carbon particles moreover were discerned either in or about these same cells.

Discussion

The above studies when considered with our previous finding that all dietary-derived cholesterol enters the blood as an insoluble increment of a chylomicron[10] appears to lead to one conclusion, namely that the hepatic reticuloendothelial cell plays an important role in ridding the blood of chylomicra and the cholesterol and lipid[2] contained therein. When this apparent mode of chylomicron ingestion is interfered with by the *simultaneous* ingestion of various other particulate substances by the Kupffer cells, a retention in plasma of chylomicra with a consequent turbidity, hyperlipemia and hypercholesteremia results. However, the latter phenomena will not occur unless precautions are taken to insure that the "blocking" agent, whether colloidal ink, iron or chromium phosphate,[1] is being injected *at the very same time* that cholesterol is being absorbed.

Cholesterol that is manufactured *exclusively* by the body itself, being in a soluble form in plasma, apparently "bypasses" the hepatic reticuloendothelial cells to enter directly, perhaps by diffusion, the hepatic parenchymal cells. Accordingly, experimental interference with the Kupffer cell does not retard the egress of such cholesterol from the plasma.

Heretofore some investigators have not been impressed with the various phenomena dealing with dietary-derived cholesterol because, considering the latter identical with the steroid synthesized in the body, they believed it was but a small increment of the total cholesterol available to the animal. However, with the availability of the present data, it is clear that dietary-derived cholesterol not only exists in the blood (for a time at least) in a different physicochemical state than endogenously derived cholesterol, but also to a certain extent is handled physiologically differently from endogenously derived cholesterol. The arterial wall of the animal, moreover, is exposed in one case to a particle, in the other, to a molecule or ion. Its reaction to either, of course, may be totally different. This difference might have pathogenetic significance in respect to atherosclerotic mechanisms.

Summary

The hepatic reticuloendothelial system of the rat appears to play an important role in the disposition of dietary-derived cholesterol but apparently is not involved in either the synthesis or disposition of endogenously derived cholesterol. The studies suggest that the difference in the physicochemical state of dietary as compared with endogenously derived cholesterol may account for the participation of the hepatic reticuloendothelial system in the disposition of the former only.

Sumario Español

El posible papel del sistema reticulo-endotelial hepático en el síntesis y disposición del colesterol endógeno fué estudiado en la rata por varios medios. Nuestros resultados sugieren que este sistema no sintetiza cantidades significativas de colesterol ni participa en el traspaso del colesterol endógeno del plasma al higado. Sinembargo, juega un papel posiblemente indispensable en purificar la sangre de colesterol derivado de la dieta.

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Phonocardiography in Patent Ductus Arteriosus

By Olga M. Haring, M.D., Aldo A. Luisada, M.D., and Benjamin M. Gasul, M.D.

The study of 28 patients proved that patients with uncomplicated patent ductus arteriosus have a typical phonocardiographic picture. This consists of a single late systolic-early diastolic murmur which may be either continuous or noncontinuous. These patients also have no electrocardiographic evidence of right ventricular hypertrophy and no elevation of pulmonary arterial pressure. Atypical murmurs are found only when additional aortic or pulmonic lesions or severely elevated pulmonary pressure due to intrapulmonary vascular changes is present. The high percentage of atypical or complicated ducti in infancy explains why infants frequently have atypical murmurs. Phonocardiography increases the accuracy of diagnosis.

In many congenital heart diseases, diagnosis can be made without resorting to cardiac catheterization or angiocardiography. "The latter procedures are useful adjuncts but by themselves seldom give the correct answer. Furthermore, they are not innocuous procedures; therefore, they should not be used routinely, but only to obtain specific information on some particular point."[1] The diagnosis of uncomplicated patent ductus arteriosus can almost always be made by auscultation. However, the accuracy of auscultation is somewhat impaired by several limitations of the human ear[2] and, moreover, cannot give information about low-pitched sounds, the exact timing of murmurs, and the configuration of the murmurs.[3] Phonocardiography, on the other hand, especially if performed in close connection with and under the guidance of the stethoscopic examination, is able to supply all the above information and may be a useful tool for diagnosis.

We have tried to find out if any typical phonocardiographic pattern might be useful for diagnosis in congenital heart diseases, starting with patent ductus arteriosus. Therefore, a series of observations, based upon graphic studies of the heart sounds and murmurs was started. Correlation of these with all other clinical and laboratory data, and confirmation of diagnosis by thoracic exploration or autopsy, was a necessary complement of the study.

This paper presents the results of the study of 28 cases of patency of the ductus which were confirmed by surgery or autopsy, all other cases having been discarded.

History

Comprehensive and systematic studies of phonocardiography in congenital heart diseases are not available. More numerous are studies in cases with patency of the ductus. Their mention should be preceded by that of the auscultatory findings on account of the close connection between auscultation and phonocardiography.

Clinical diagnosis of patency of the ductus was first reported by Bernutz in 1847. Reliable clinical observations are rare in the following years so that only 20 cases were published until 1893.[4] It is interesting, but not accidental, that the great majority of the cases reported up to that time had cardiac failure or pulmonary hypertension; this conclusion can be reached by reviewing the findings in the light of our present knowledge.

In 1849 Skoda[5] described the typical murmur of patent ductus as "a continuous murmur with systolic reinforcement" best audible over the pulmonic area. In 1867 Gerhardt[6] stated that, although the murmur may vary considerably in intensity, it usually has a systolic accentuation and continues into

From the Cardio-Physiologic Department, Cook County Children's Hospital, and the Hektoen Institute for Medical Research; and from the Division of Cardiology, The Chicago Medical School and Mount Sinai Hospital of Chicago, Ill.

diastole. He also described a decrease of intensity of the murmur following sustained inspiration. On the other hand, several other investigators noted only a systolic murmur.[7-9] More recent publications again mention the possibility that the murmur may be only systolic. Abbott[10] stated that ". . . the presence of a patent ductus is not always marked by adventitious sounds; when murmur is present, it may be short and systolic in rhythm." Taussig[1, 11] mentions that, in infancy and early childhood, patency of the ductus usually causes only a systolic murmur.

When routine physical examination became more widespread, patency of the ductus was recognized as the second most frequent congenital abnormality. Occasional diagnostic errors were still demonstrated by autopsy.

Following successful ligation of the ductus by Gross,[12] accurate diagnosis became even more imperative on account of the possible danger which may result to the patient by either an exploratory thoracotomy or undue delay of surgery.

Patency of the ductus with normal pulmonary pressure and patency of the ductus with elevated pulmonary pressure (so-called reversed shunt) have been established as two separate clinical syndromes, with the help of cardiac catheterization. The second group, however, includes only about 5 per cent of the cases.

The murmur of patent ductus is its most distinctive feature and a reliable diagnosis can be made if this is present, even in the absence of any other symptoms or signs. Routier[13] in France was the first investigator to record this murmur graphically, demonstrating the murmur in 14 patients between the ages of 4 and 47. In 1943 Hubbard[14] published another phonocardiographic study of patent ductus. Without mentioning the number or ages of his patients, he stated that "the records are so distinctive as to permit diagnosis from examination of the tracing alone." Routier, as well as Hubbard, found both systolic and diastolic vibrations. Hubbard observed a late systolic, while Routier mentioned an early diastolic accentuation of the vibrations. In several textbooks and studies[2, 3, 15-20] phonocardiograms with a continuous murmur which has either a late systolic or an early diastolic accentuation and which "rides over the second sound" are reproduced.

Hultgren and coworkers[21] presented eight cases of patent ductus with pulmonary hypertension. The phonocardiograms of six cases were supposed to reveal only a systolic murmur. However, diastolic vibrations can be seen in three patients, even though atypical.

Reinhold and Nadas[37] found a crescendo late systolic murmur in all typical cases with patent ductus and in five of seven atypical cases.

Material and Method

The present study deals with a group of 28 patients in whom the clinical diagnosis of patent ductus was confirmed by surgery in 25, by autopsy in two, and both by surgery and autopsy, in one. Twenty-four were studied at Cook County Children's Hospital,* and three at Mount Sinai Hospital of Chicago, while one is a case who died at Beth Israel Hospital, Boston.

Before undergoing surgery,† all patients were studied by means of x-ray, fluoroscopy, electrocardiography, and phonocardiography; 13 were also studied by cardiac catheterization and most of them, by angiocardiography. Most phonocardiographic tracings were taken with a Sanborn Twinbeam Cardiette, the others with the Sanborn Stethocardiette. Recordings were made over the usual auscultatory areas (apex, midprecordium, pulmonic, aortic, tricuspid areas) with the stethoscopic and logarithmic devices. Regional low-frequency tracings with the linear microphone were also taken.

Age and Sex. One patient was 5 months old, another, 12 months old and still another, 14 months old. Altogether, 11 cases were 5 years of age or younger. Eight cases were between 5 and 10; four were between 10 and 20; two between 20 and 30; and 3 between 30 and 40 years of age. There were 24 females and 4 males.

Diagnosis. The diagnosis of patent ductus was made in every case prior to surgery. Three patients also had coarctation of the aorta, three had a small ventricular septal defect, and one had a slight pulmonic stenosis.

* Catheterization studies were done by Drs. D. Fischer or R. Dillon.

† All surgical cases were operated on by Dr. E. F. Fell of the Cook County Hospital except two cases which were operated on by Dr. S. Mackler of Mount Sinai Hospital.

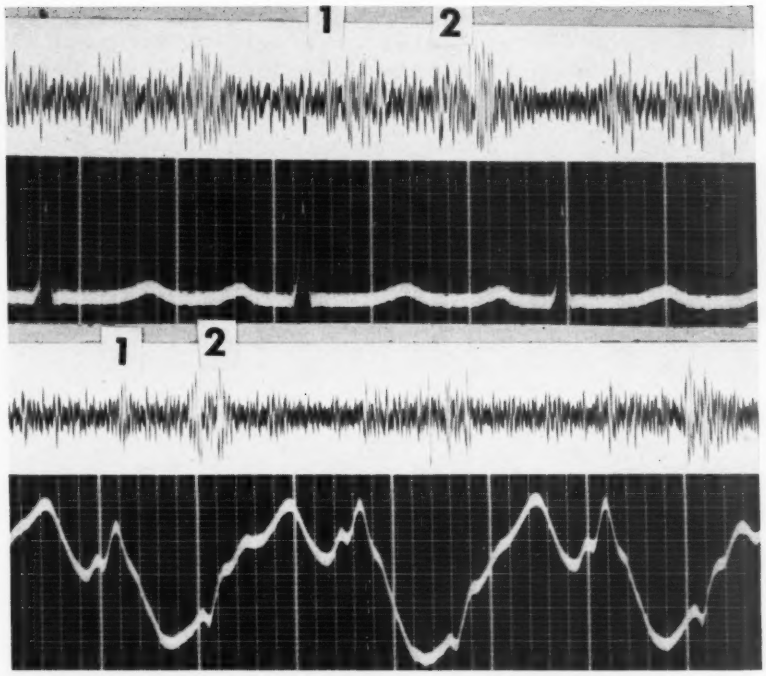

FIG. 1. Typical continuous murmur (Case 7). The phonocardiogram taken at the pulmonic area shows a continuous murmur throughout systole and diastole: it has a systolic accentuation and overrides the second sound. (A) Stethoscopic tracing and electrocardiogram in lead II. (B) Logarithmic tracing and jugular tracing.

RESULTS

A summary of the data of 28 patients between the ages of 5 months and 38 years is given in table 1.*

Phonocardiograms

The findings in tracings recorded at the pulmonic area, apex, and aortic area, are separately analyzed.

(A) *Pulmonic Area.* A typical murmur was present in 24 of the 28 patients. In 13 patients there was *a continuous murmur* throughout systole and diastole while in the other 11, either the systolic or the diastolic component (more frequently the latter) was shorter. *A late-systolic crescendo plus early-diastolic decrescendo murmur was considered typical of patent ductus*, as described in previous graphic studies. In 13 patients, the murmur started right after the first sound and terminated only before the following first sound; in 11 patients, there was a pause before and after the first sound. Therefore, a distinction was made between the "typical, continuous" (fig. 1) and the "typical, noncontinuous" murmur (fig. 2). One patient who presented a typical, continuous murmur was 5 years old; one with occasionally continuous murmur was 4½ years old, while the other 11 were above 5 years. Eight patients with typical, noncontinuous murmur were under 5 years of age: the youngest was 5 months old, one was 1 year old, another 14 months old, and two were 2 years old. An atypical murmur was found in only 4 out of 28 patients (table 1, cases 11, 12, 15 and 24* and fig. 3).

(B) *Apex.* A systolic murmur of irregular configuration, made of both low and high-pitched vibrations, was recorded in every

* At the request of the Editor, table 1 is being omitted. This table will be furnished on request.

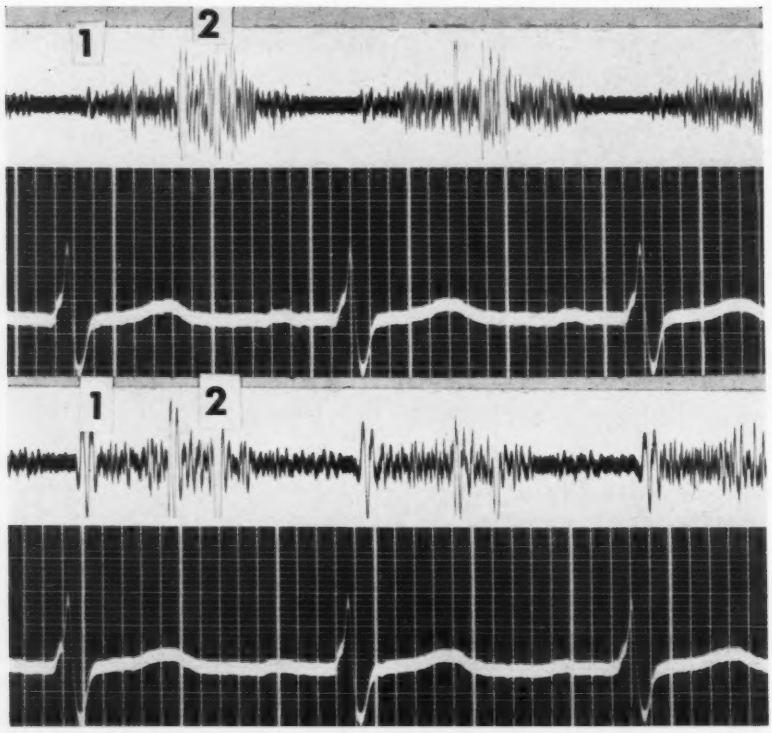

FIG. 2. Typical noncontinuous murmur (Case 19). The phonocardiogram taken at the pulmonic area shows a systolic crescendo-diastolic decrescendo murmur overriding the second sound. The same murmur, recorded at the aortic area, shows transmission of mainly the systolic component. (A) Pulmonic area, stethoscopic tracing and electrocardiogram in lead II. (B) Aortic area, stethoscopic tracing and electrocardiogram in lead II.

case. An early diastolic murmur, with "decrescendo" character and consisting mostly of high-pitched vibrations, was registered in seven patients (cases 1, 2, 5, 14, 16, 17 and 22); a loud, irregular, presystolic murmur was recorded in four patients (cases 9, 3, 14 and 15). Two patients (cases 21 and 19) had a loud third sound. It should be noted that both had a rapid heart rate when studied.

(C) *Aortic Area.* A systolic murmur was registered over this area. This was similar in character to that registered at the apex but was of longer duration, lasting in the majority of cases through the entire systole. In 18 of the 28 patients, a diastolic murmur was also present; it started immediately after the second sound; it was of a somewhat irregular character, and consisted mostly of high-pitched vibrations. One patient had a loud fourth (atrial) sound (case 24). The second sound was split in eight patients (cases 1, 2, 4, 17, 18, 19, 22 and 23) and was markedly decreased in one (case 12).

Description of Findings in the Atypical Cases

Case 11. N. G., a 9 year old female, had a clinical diagnosis of patent ductus with pulmonary hypertension (Table 1*). The phonocardiogram showed a short, early systolic, and an early diastolic decrescendo murmur at the pulmonic area, both consisting of high-pitched vibrations. At the aortic area, there was an all-systolic murmur with irregular vibrations, and, at the apex, a short systolic murmur, similar in character to that recorded at the aortic area. The electrocardiogram showed both right and left ventricular hypertrophy. Autopsy

* See footnote page 503.

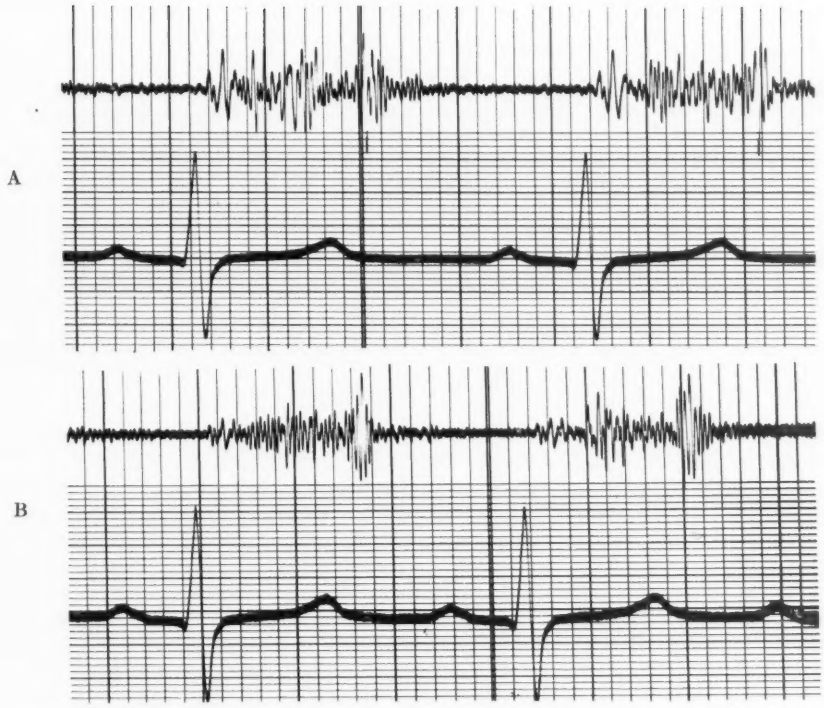

FIG. 3. Atypical murmur (Case 12). The phonocardiograms recorded at the pulmonic area show an all-systolic, atypical murmur and a short, early-diastolic decrescendo murmur, also not typical for patent ductus. (A) Stethoscopic tracing over pulmonic area and electrocardiogram in lead II. (B) Logarithmic tracing over pulmonic area and electrocardiogram in lead II.

showed a short ductus, a severely enlarged pulmonary artery and hypertrophy and dilatation of both ventricles.

Case 12. H. F., a 9 year old male, had a clinical diagnosis of patent ductus plus coarctation of the aorta (table 1*). The phonocardiogram showed an all-systolic murmur and an early diastolic, decrescendo murmur at the pulmonic area (fig. 3). There was an all-systolic murmur with irregular vibrations at the aorta and at the apex; also, a weak second aortic sound. The electrocardiogram suggested both right and left ventricular hypertrophy. Surgery revealed the existence of the clinically diagnosed lesions. The patient was successfully operated on.

Case 15. B. D. was a 38 year old male. The clinical diagnosis was patent ductus plus coarctation of the aorta (table 1*). The phonocardiogram at the pulmonic area showed irregular, late-systolic and early-diastolic vibrations. There also was an atrial type of triple rhythm. The tracing made at the aortic area showed an all-systolic plus an early-diastolic murmur, similar in character to that recorded at the pulmonic area. At the apex, there was an all-systolic and a presystolic murmur. The electrocardiogram revealed both right and left ventricular hypertrophy. Autopsy revealed the coarctation and the ductus and bilateral ventricular hypertrophy.

Case 24. S. D. was a 3 year old female. The clinical diagnosis was patent ductus. The phonocardiogram at the pulmonic area showed a diamond-shaped, systolic murmur and a high-pitched, early diastolic murmur; the second pulmonic sound was split. The same murmurs were recorded at the aortic area, while the apex showed only the diamond shaped, systolic murmur. The electrocardiogram suggested right ventricular hypertrophy. Following surgery, catheterization was performed because of the persistence of a systolic murmur. Slight pulmonic stenosis was recognized.

In all cases where a typical murmur was recorded at the pulmonic area, the second sound appeared distinctly within the vibrations of the murmur.

Electrocardiogram

Analysis of the tracings of the 28 patients showed that they belonged to one of the following three electrocardiographic groups: (1) normal tracing; (2) left ventricular hypertrophy; (3) left and right ventricular hypertrophy.

Group 1.—*Normal tracings* were present in eight patients, seven of whom had patency of the ductus as the sole congenital anomaly, while one (case 19) also had a small ventricular septal defect. Catheterization data, available in two of these patients, revealed normal or borderline right ventricular pressures.

Group 2.—*Pattern of left ventricular hypertrophy* was found in 15 patients, two of whom also had a ventricular septal defect (cases 3 and 7). Cardiac catheterization, done in nine of these cases, revealed slightly elevated right ventricular pressures in four (cases 1, 3, 7 and 9).

Group 3.—*Pattern of right and left ventricular hypertrophy* was found in five patients (cases 11, 12, 14, 15 and 24). In three of them, autopsy confirmed the type of hypertrophy indicated by the electrocardiograms (cases 14, 15 and 11) while catheterization revealed markedly elevated right ventricular pressures in the other two (cases 12 and 24).*

Discussion

The graphic characteristics of the murmur caused by patency of the ductus, as described by Routier and confirmed by others, set this murmur apart from those caused by valvular lesions. It is seldom appreciated that all murmurs due to valvular lesions are strictly limited by the phases of valvular action; they are either systolic or diastolic. Even when a complex valvular lesion causes a double murmur, the following characteristics can usually be recognized (fig. 4):

(a) *Mitral murmurs.* The *systolic* murmur is poorly transmitted to the pulmonic area; in general, it has low vibrations in late systole before the second sound. If there is a *mid-diastolic* murmur, this is clearly separated from the second sound. Therefore, the second pulmonic sound, which is usually loud, is clearly separated from both the systolic and the diastolic vibrations.

(b) *Pulmonic murmurs.* If there is pulmonic stenosis, the *systolic* murmur may last throughout systole and reach the second sound; this, being weak, may not be visible. However, there usually is *no diastolic* murmur and the vibrations terminate coincident with the end of the T wave. If there is pulmonic insufficiency, the *diastolic* murmur starts after the second sound; the latter, however, is separated from systolic vibrations.

(c) *Aortic murmurs transmitted to the pulmonic area.* In general, the systolic murmur is diamond shaped and decreases before the second sound. This is loud because it is a second pulmonic sound. The early-diastolic, aortic murmur starts soon after the second sound or sometimes later. The second sound

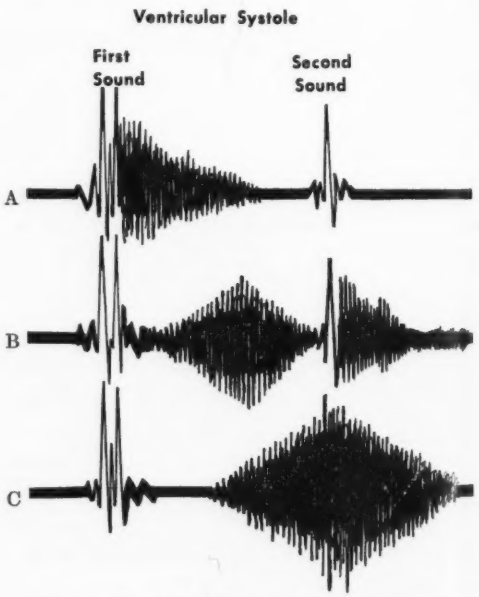

Fig. 4. Sketch of different types of murmurs. (A) Systolic decrescendo murmur of mitral insufficiency. (B) Systolic diamond-shaped murmur of aortic or pulmonic stenosis, and early-diastolic murmur of aortic or pulmonic insufficiency. (C) Systolic-diastolic murmur of patent ductus (noncontinuous type).

* In the last case, catheterization was performed only after surgery; therefore, the findings are not reported in the table.

is usually separated from the systolic murmur, or from the diastolic, or from both.

Therefore, the only cases where no sharp limitation can be found are those with multiple murmurs (mitral, aortic, pulmonic) and a faint second sound. These cases, which are rather unusual, have clinical pictures which are quite different from those of patent ductus.

(d) Both *atrial* and *ventricular septal defects* are accompanied by a murmur which is of lesser intensity at the end of systole and is sharply terminated by a loud second sound. The rare cases where a septal defect has an associated pulmonic or aortic insufficiency have *two murmurs*, one systolic and the other early-diastolic, with a loud second sound dividing the two and preceded by a pause or a zone of low vibrations.*

Therefore, most valvular lesions and the septal defects have murmurs with different characteristics from those found in another group of cardiovascular conditions: (a) patent ductus arteriosus; (b) aortic septal defect; (c) coarctation of the aorta; (d) arteriovenous fistula of the lung; (e) arteriovenous fistula of other vessels.

The murmur of the arteriovenous *fistulas*, including those of the lungs, is observed in various areas of the chest, neck, or limbs, but not over the pulmonic area.† The murmur of *coarctation of the aorta* is frankly *systolic* over the pulmonic area and the back upon auscultation, even though diastolic vibrations may be found in phonocardiograms recorded over the back.[23]

The venous hum has the following characteristics: (a) it is soft and high-pitched; (b) it usually has the maximum intensity over the right supraclavicular space; (c) if recorded over the precordium, it is louder at the right than at the left of the sternum; and (d) it is highly modified by changes in position of the patient or of the patient's head.

The murmurs of both *patent ductus* and the *aortic septal defect* have a common mechanism: they are caused by a shunt connecting two arterial vessels. The blood may pass through the shunt during the entire cycle and the only reason for an acceleration of flow and an intensification of the murmur is a greater gradient of pressure between the two vessels. In aortic septal defect, the coincidence of the two pressure pulses with the cardiac cycle is greater on account of the proximity to the ventricles; therefore, the highest flow takes place at the peak of the aortic pulse which is usually at the middle or in the second half of systole and the murmur may be louder over the third intercostal space.[35, 36]

A special case should be made for the *distal aortopulmonary fistula*. This actually represents an extremely short ductus. The gradient of pressure between aorta and pulmonary artery is the same as in the case of a ductus but the shortness of the channel may somewhat change the type of murmur. Moreover, pulmonic insufficiency may also be present on account of the severity of the shunt and of pulmonic hypertension.[22]

In *patent ductus*, the following factors play a role:

(a) The peak of the aortic pulse occurs later on account of the transmission time between left ventricle and the end of the aortic arch: this peak is very near the second sound.

(b) The time necessary for the blood to pass through the ductus causes a further additional delay, so that the maximal flow is likely to occur at the time of the second sound.

(c) The extremely low level (5 to 10 mm. Hg) of pulmonic diastolic pressure in comparison with the aortic diastolic pressure creates a suction which prolongs the flow through the ductus, a fact which is particularly apparent during inspiration, as observed by François-Frank.

Therefore, the murmur of patent ductus, is loudest in the first and second intercostal spaces (that of aortic septal defect is loudest in the third space), and typically "rides over" the second sound. Thus, it is incorrect to

* Such a murmur was present in a case presented by Morgan and Burchell[38] where other clinical data simulated patency of the ductus.

† An exception is represented by *arteriovenous fistula of the coronary vessels* which presents a continuous murmur over the precordial area.[39, 40] This lesion however, is extremely rare and is accompanied by typical changes of the electrocardiogram.

describe such murmur as systolic and diastolic, as is usually done: *it is either a continuous or a late systolic—early diastolic murmur and it has either a late-systolic or an early-diastolic accentuation.*

It should be noted that infants or young children with a ductus may have a purely systolic murmur, *not because of their age but because of unusual conditions of pressure.* It is logical to expect that a high pulmonic diastolic pressure will change the characteristics of the murmur by decreasing the gradient between aortic and pulmonic pressure, especially during diastole. This possibility was demonstrated by some of the cases of Hultgren. It should be noted that, among our cases, older children and adults had a typical, continuous murmur, while infants and young children had a typical, noncontinuous murmur. This interruption of the murmur may contribute to the auscultatory impression of only a systolic murmur. Moreover, the second sound, being within the murmur, may not be accurately heard, and the murmur may seem only systolic. Aortic pressure is lower in infants; this causes a less important gradient between aorta and pulmonary artery and may explain the intermittent flow (late systolic–early diastolic). Whenever the ductus is complicated by valvular, aortic, or pulmonary lesions, the gradient of pressure between aorta and pulmonary artery may vary; there may be equalization of pressure or even reversal of flow. Moreover, heart failure may decrease the gradient of pressure.[27, 33] It is natural then to expect completely atypical murmurs.[27, 33, 34] These complex or atypical cases are chiefly encountered among infants on account of their higher mortality and have contributed to the clinical impression of a high percentage of atypical murmurs in infants. Adults with secondary pulmonary complications may also experience such an increase of pulmonary pressure.

Correlation among the Murmurs at the Pulmonic Area, Electrocardiographic Pattern and Intracardiac Pressures

A very definite correlation was found between the type of murmur found at the pulmonic area, the electrocardiographic pattern, and the intracardiac pressures in each case.

(A) *Typical murmurs.* Twenty-three patients (out of 24 with typical murmurs) had either a normal electrocardiogram, with or without left axis shift, or showed evidence of left ventricular hypertrophy. Only one case had a right focal block besides the electrocardiographic signs of left ventricular hypertrophy (case 14). The patient died of cardiac failure; autopsy revealed minimal coarctation of the aorta and hypertrophy of both ventricles. In the 11 cases where cardiac catheterization was performed, the right ventricular systolic pressures were found normal in six patients and slightly elevated in five patients.

(B) *Atypical murmurs.* The four patients with atypical murmurs showed marked right and left ventricular hypertrophy in their electrocardiograms (cases 11, 12, 15 and 24). Cardiac catheterization performed before surgery showed moderately elevated pulmonary pressures in one patient (case 12) and markedly elevated pressures in the other (case 11). Case 24 was not catheterized before surgery, when only a patent ductus was diagnosed, but after ligation it appeared necessary to do catheterization because of a persisting systolic murmur at the pulmonic area. Elevated pressure was found in the right ventricle and the diagnosis of pulmonary stenosis was made. Case 15 was not operated on. At autopsy, coarctation of the aorta, a wide, short, and calcified ductus, and hypertrophy of both ventricles was found.

Correlation between the Murmurs at the Pulmonic Area and the Cardiovascular Lesions

Out of 24 patients with *typical murmurs,* only four had lesions in addition to patency of the ductus (three had a small interventricular septal defect and one had coarctation of the aorta).

Out of four patients with *atypical murmurs,* two had an additional coarctation of the aorta, one had pulmonary stenosis, and one had pulmonary hypertension due to vascular changes and marked hypertrophy of both ventricles.

Therefore, a close relationship among

cardiac dynamics, murmurs, electrocardiogram, and intracardiac pressures was found. This confirms previous observations of Cabrera and coworkers,[24] Edwards and his colleagues,[25] and several other investigators.[26-31]

Uncomplicated patent ductus always has a typical murmur, no electrocardiographic evidence of right ventricular hypertrophy, and no important elevation of pressure in the pulmonary artery. Atypical murmur always means atypical ductus, having either additional cardiovascular lesions or severely elevated pulmonary pressure due to intrapulmonary vascular changes.

Conclusion

The phonocardiogram of uncomplicated patent ductus arteriosus shows a typical configuration of the murmur. This has no resemblance to that caused by valvular lesions or septal defects and is not limited by the valvular events of the heart. It is a single murmur which has either a late-systolic or an early-diastolic accentuation, and which frequently continues throughout the entire cardiac cycle. The graphic configuration of this murmur has diagnostic significance and is typical at any age. An atypical murmur is encountered if there is severe pulmonary hypertension or complicating lesions modifying the gradient of pressure or causing additional murmurs.

Infants present the highest percentage of atypical murmurs, not because of their age but because of the higher relative frequency of complex lesions and atypical ducti.

Summary

1. The phonocardiograms of 28 patients with patent ductus arteriosus were studied. They were correlated with the electrocardiograms, catheterization data, and surgical or autopsy data.

2. The typical murmur is a late systolic-early diastolic murmur. It may be either continuous or noncontinuous. Infants and young children have a noncontinuous but still typical murmur unless there are complicating lesions of the heart, vessels, or lungs.

3. The conditions causing this type of murmur and the factors of possible modification, are analyzed.

Sumario Español

1. Los fonocardiogramas de 28 pacientes con conducto arterioso patente fueron estudiados. Fueron correlacionados con los electrocardiogramas, datos de cateterismo y datos de autopsia o quirúrgicos.

2. El soplo típico es tardío en sístole y temprano en diástole. Puede ser continuo o no continuo. Infantes y niños jóvenes tienen un soplo no continuo pero no obstante es un soplo típico a menos que no existan otras complicaciones cardíacas o de los grandes vasos y pulmones.

3. Las condiciones que causan este tipo de soplo y los factores de posible modificación, son analizados.

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Liver Function and Hypertension

Blood Pressure and Heart Weight in Chronic Hepatitis

By FLEMMING RAASCHOU, M.D.

The purpose of the present work was to study the incidence of arterial hypertension in a series of autopsied cases of chronic hepatitis. The frequency of patients with hypertension, examined according to three criteria (cerebral hemorrhage, hypertrophy of the heart, and incidence of hypertension as determined by actual measurements of blood pressure during life), is essentially lower in an autopsy series consisting of women who died of or with subchronic hepatitis than in a control series of autopsied female patients with the same age distribution who died of all other diseases.

CHAUFFARD,[7] in 1892, was the first to point out that most icteric patients have a low blood pressure. About 1900, Gilbert and Garnier[11] stressed low blood pressure as a characteristic feature of cirrhosis of the liver. In 1937 Loeper[17] and in 1949 Spatt and Rosenblatt[28] made the same observation. In 1930, Geill[10] found strikingly low blood pressure values in acute, infectious hepatitis. Meakins,[18] in 1932, was the first to show that the blood pressure in patients with arterial hypertension may show a pronounced fall when these patients develop acute, infectious hepatitis, and that this low blood pressure may persist for a prolonged period after the jaundice has subsided. In normotensive patients, too, there seems to be a tendency toward a lower blood pressure when they are attacked by acute hepatitis, a finding made by Selander[24] in 1939 in a large series of patients with hepatitis.

The purpose of the present work was to study the incidence of arterial hypertension in a series of autopsied cases of chronic hepatitis. As a result of this study the hypothesis is put forward that a severely damaged liver function prevents the development of hypertension in man.

In a previous study[21] the etiologic relationship of obstruction of the urinary tract (hydronephrosis) to the development of hypertension was investigated in a series of autopsied cases. During the period of this investigation (January 1944, to January 1948) there occurred in Denmark an epidemic of hepatitis during which numerous patients died. The livers of these patients showed the gross and microscopic characteristics of subchronic atrophy of the liver.[1-4, 14] With but few exceptions the patients who died were women over 45 years of age. Death occurred, on the average, 8.2 months after the appearance of the first symptom[4] and was the result of severe, chronic hepatitis with ascites, edema, jaundice, hemorrhagic diathesis and, at last, hepatic insufficiency with hepatic coma. In this large group of women, the great majority of whom had reached an age at which essential hypertension is very frequent, the incidence of hypertension was amazingly low. It occurred to me, therefore, that in some way the severe hepatic disorder either prevented the development of hypertension in patients who were to be expected to be hypertensive or caused an already developed hypertension to subside again.

MATERIAL

This comprises a series of cases of hepatitis and a control series. In the course of the period mentioned in the preceding paragraph, 108 patients with subchronic atrophy of the liver were autopsied in Kommunehospitalet, Copenhagen; 102 were women. Since so few males died of this disease, only the series of women has been analyzed. The age incidence in the female patients is shown in figure 1: the curve rises abruptly after the forty-fifth year, the summit occurring between 65 to 75 years. The control series comprises 93 unselected women over 45 years of age who died during the same period and came to necropsy. The patients of this series died of many

From Department III, Kommunehospitalet, Copenhagen, Chief: Senior Physician Poul Iversen, M.D. and from the Institute of Pathology of Kommunehospitalet. Chief: Svend Petri, Prosector, M.D.

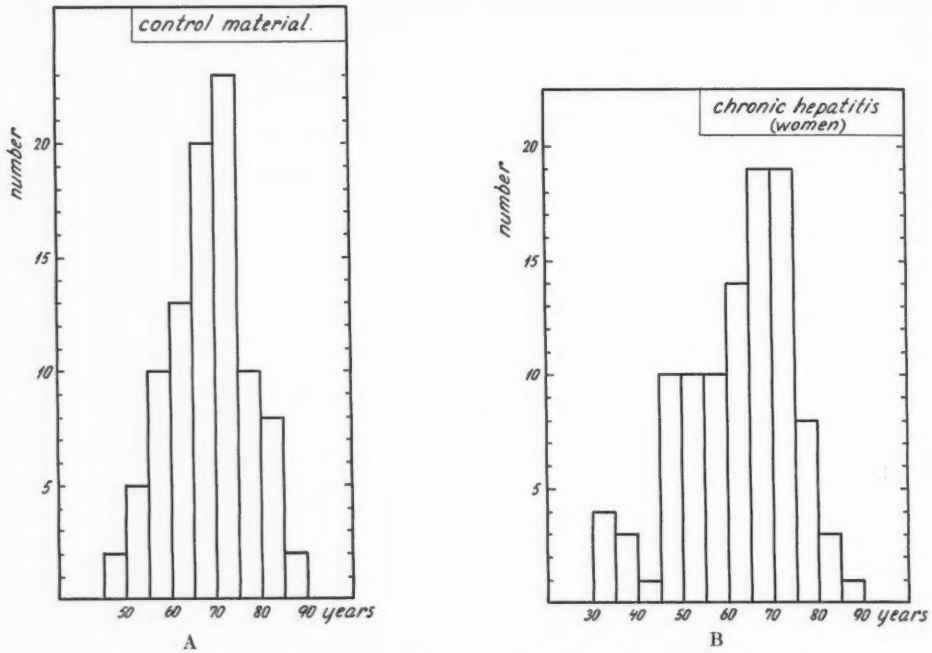

FIG. 1. Subchronic atrophy of the liver and control material. Age distribution.

diseases, but none of them had subchronic atrophy of the liver; patients with hypertrophy of the heart considered to have been caused by affections other than essential hypertension (e.g., valvular heart disease, chronic glomerulonephritis, chronic cor pulmonale, pheochromocytoma) were retained in both series. The age incidence in the control series corresponds fairly well with that of the series of cases of hepatitis (fig. 1).

The incidence of hypertension was examined in the two series, and the following three criteria were used in determining the presence or absence of hypertension: (1) The frequency of cerebral hemorrhage, (2) the frequency of hypertrophy of the heart, and (3) the frequency and degree of hypertension as shown by the recorded blood pressure determinations in the patients.

RESULTS

Incidence of hypertension in patients with hepatitis

(1) *The Occurrence of Cerebral Hemorrhage in the Two Series.* None of the patients with hepatitis died of cerebral hemorrhage, whereas 11 patients in the control series (11.8 per cent) died of this condition.

(2) *Frequency of Hypertension as Determined by the Finding of Hypertrophy of the Heart at Necropsy.* Hearts weighing more than 400 Gm. were considered to be hypertrophied. Figure 2 shows the distribution of heart weights in 95 female patients with subchronic atrophy of the liver and in 93 women over 45 years in the control series. Five out of 95 women (5.3 per cent) with subchronic atrophy of the liver had hearts which weighed more than 400 Gm.; the average weight of these five hypertrophied hearts was 425 Gm. In the control series there were 33 out of 93 women (35.5 per cent) whose hearts weighed more than 400 Gm. the average weight being 475 Gm.

The number of cases with hypertrophy of the heart was thus about seven times greater in the control series than in the series with hepatitis, and the hypertrophied hearts in the control series weighed on an average 50 Gm. more than those found in the case of hepatitis.

(3) *Frequency and Degree of Hypertension, as Determined by Actual Measurements during Life.* This criterion is defective because not all the patients had had their blood pressure measured. However, since 89.2 per cent in the

control series and 83.4 per cent in the series with hepatitis had had their blood pressure measured, and as it was apparently quite accidental that no such measurement had been performed in the other cases, it was considered justifiable to draw certain conclusions from this part of the investigation.

(a) *Systolic blood pressure.* In the series of patients with hepatitis 15 (or 17.7 per cent) had pressures of 160 mm. Hg or higher, and three (or 3.5 per cent) had systolic pressures of 180 mm. Hg or higher. The corresponding figures in the control series were: 39 patients (47 per cent) with pressures of 160 mm. Hg or higher and 21 (25.3 per cent) with pressures equal to or above 180 mm. Hg. From these findings it can be concluded that if 160 mm. Hg is accepted as the lower limit of elevated systolic blood pressure, the number of hypertensive patients is about three times greater in the control series, than in the hepatitis series, and if 180 mm. Hg is accepted as the lower limit of systolic hypertension, the number is about seven times greater in the former series than in the latter. In both instances the average blood pressure of the hypertensive patients is higher in the control series than in the series with hepatitis.

(b) *Diastolic blood pressure.* The same conclusions can be drawn from an examination of the diastolic blood pressure. If 100 mm. Hg is fixed as the lower limit of diastolic hypertension, the series of cases of hepatitis contains 12 patients (or 14.8 per cent) whose pressures were over this value; but if 120 mm. Hg is accepted as the beginning of diastolic hypertension, only one patient (1.2 per cent) had too high a diastolic pressure. In the control series 21 patients (or 26.3 per cent) had pressures above 100 mm. Hg, and nine (11.3 per cent) had pressures over 120 mm. Hg. This analysis of the diastolic pressure, suggests that the severe cases of hypertension do not occur in the patients with hepatitis.

The chief *conclusion* of this analysis is that the frequency of patients with hypertension, examined according to the three criteria mentioned above (cerebral hemorrhage, heart weight and incidence of hypertension), is essentially lower in an autopsy series consisting of women who died of or with subchronic hepatitis than in a control series of autopsied female patients with the same age distribution who died of all other diseases. Severe, diastolic hypertension practically does not occur in patients with this disorder of the liver.

Of the three criteria, the first two (cerebral hemorrhage and heart weight) are presumably the most important, since these could be studied in the whole series of patients. With regard to the criterion of blood pressure as measured during life, its value is diminished, first, as already mentioned, because one-tenth to two-tenths of the patients of our series had not had their blood pressure measured, and second, because the number of blood pressure determinations in the individual patients varied greatly. The incidence of hypertension found in the control series agrees fairly well with the expected incidence in an average population. Robinson and Brucer[23] assumed that the incidence of hypertension in adults is at least 40 per cent, and Søbye[29] stated that a hereditary predisposition to hypertension was found in about 30 to 40 per cent of the population.

Possible Alleviation of Hypertension after Development of Hepatitis

If unquestionable cases of permanent hypertension which disappeared when the patient developed chronic hepatitis can be demonstrated, this will lend support to the hypothesis of a causal relationship between severe hepatic disorders with reduced liver function and the low incidence of hypertension. All case records in the hepatitis series have been gone through

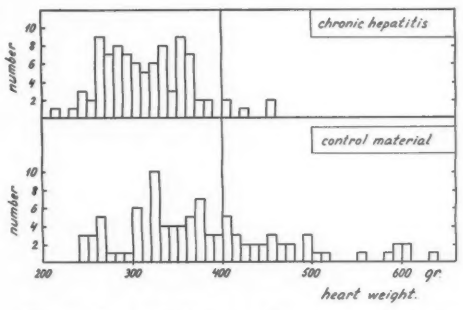

FIG. 2. The distribution of heart weights in the hepatitis and control material.

with a view to this, and only the following case could be found. It may be mentioned that, with regard to the blood pressure of these patients with hepatitis, unfortunately prehepatitis details often were not available.

M. E. B. was a woman 68 years of age. (Department III, Kommunehospitalet, case record no. 1468/1946, and the Institute of Pathology, case record no. 817/1946.) She gave the following history. Since 1936 (her fifty-eighth year) the patient had been suffering from dyspnea on exertion, restlessness and precordial pain usually due to emotional disturbance, and had also had a tendency to edema of the ankles in the evening. In 1938 hypertension (210 to 250 mm. Hg systolic pressure) was first recorded. In 1941 the blood pressure ranged between 280/180 and 220/140. On March 15, 1946, it was 240/150. In June, 1946, the patient became ill with fatigue, dyspepsia and slight jaundice. She was admitted to Department III of Kommunehospitalet, where she remained from Aug. 29 to Oct. 24, 1946. The diagnosis was chronic hepatitis. She developed ascites and edema of the leg, and had anemia, a positive Takata-Ara test and a positive thymol test. In the course of the disease of the liver the following blood pressures were measured: 170/110 on August 15, 160/90 on September 2, 140/90 on September 5, 165/95 on October 18, 135/75 on October 21. An electrocardiogram (Aug. 30, 1946) showed only left axis deviation; a roentgenogram of the heart (Sept. 10, 1946) showed the width of heart to be 14 cm. and of the thorax, 26 cm. There was slight hypertrophy of the left ventricle.

On Oct. 24, 1946, about five months after the appearance of the first symptom, the patient died of hepatic insufficiency with hepatic coma. Necropsy showed subchronic atrophy of the liver, severe ascites, slight jaundice, enlargement of the spleen, and moderate pulmonary edema. The heart weight was normal (310 Gm; body weight: 61 Kg.). The wall of the left ventricle measured 15 mm.

Comment. This case was thus one of hypertension of at least eight years' duration in which a high diastolic pressure had been recorded. When this patient developed chronic hepatitis, an essentially lower blood pressure was found, and at necropsy there were no signs of hypertrophy of the heart.

Discussion

The question that immediately arises is whether the low incidence of hypertension in this severe hepatic disorder is specific and, therefore, attributable to special biochemical changes in the blood which determine the low blood pressure, or whether it is due to nonspecific causes, such as, for instance, impairment of general health, emaciation or other factors incidental to such disease. It may be mentioned in this connection that hypertension is seldom seen in various forms of cancer presumably owing to the cachexia which develops.[16]

The Role of the Liver in Experimental, Renal Hypertension

That the liver plays such a role is strongly suggested by work such as that of Braun Menendez and colleagues.[6] In all probability hypertensinogen is produced in the liver[15, 19] since the content of hypertensinogen in the blood of normal and hypertensive dogs is reduced or disappears completely after hepatectomy or injury to the liver (by carbon tetrachloride and ethyl alcohol). Moreover Haynes and Dexter[12, 13] found that the content of hypertensinogen was reduced in human plasma in six out of nine patients with hepatic insufficiency. Renin, likewise, is generally considered to be destroyed, in part at least, in the liver since hepatectomy will delay its removal from the blood.[15] Likewise *hypertensinase*, the hypertensin splitting enzyme, is also said to be present in liver as well as in many other parts of the organism; however, its concentration in the blood is said not to be changed in hepatic insufficiency.[13]

Shorr and associates[25] put forward another theory about the occurrence of two antagonistic substances: vasoexcitor material (VEM) and the vasodepressor material (VDM), the function of which should be to regulate the peripheral blood flow and blood pressure. Vasodepressor material is produced in the liver, the spleen and the skeletal muscles in the case of tissue anoxia, and is destroyed in the liver under aerobic conditions. These authors found increased quantities of vasodepressor material in the blood and the liver tissue of rats with experimental cirrhosis of the liver; increased proportions of vasodepressor material are also said to be found in the blood of patients with cirrhosis of the liver.[27]

Finally, it may be mentioned that recently

Davis and co-workers[8, 9] have published the results of experiments on dogs subjected to the Goldblatt procedure which, both with regard to the procedure and the results of experiments, closely resemble the experiments on dogs, which have been reported by Raaschou and Trautner[22] in Goldblatt dogs; Davis and co-workers have undertaken partial clamping of the portal vein and the hepatic artery, either separately or simultaneously. When the flow of blood through the liver had been sufficiently reduced (which manifested itself, *inter alia*, by the appearance of fatty infiltration in the liver), they observed that the blood pressure fell.

The strikingly low frequency of arterial hypertension in subchronic atrophy of the liver, and the fact that the function of the liver is found to be normal in essential hypertension in man,[5] form the basis of the hypothesis on which the experimental work of Raaschou and Trautner[22] was based: a normal or only slightly damaged liver function is a necessary condition for the development of hypertension in man, whereas a severely damaged liver function will prevent the development of hypertension or eliminate already existing hypertension. The object of Raaschou and Trautner's work was to study in dogs the effect of a severe hepatic injury (caused by obstruction of the common bile duct) upon previously produced experimental renal hypertension. Briefly, it can be said that six hypertensive dogs (with experimental renal hypertension produced according to Goldblatt's method), four with hypertension of short duration, two with more prolonged hypertension, displayed a gradual fall in the blood pressure toward, or to the normal preoperative values after obstruction of the common bile duct had been established. These falls in the blood pressure were observed in dogs which had been in good health and which were sufficiently fed. In one normotensive dog the obstruction of the common bile duct produced no material changes in the blood pressure. The cause of the fall of the blood pressure after obstruction of the common bile duct could not be explained, but the experimental results are in accord with the clinical experience which has been summarized in this paper.

Summary

A comparison with regard to the incidence of arterial hypertension has been made between an autopsy series consisting of 102 women who had died of chronic hepatitis (subchronic yellow atrophy of the liver) and a control series of autopsied patients who did not have liver disease. By means of three criteria of arterial hypertension [(1) the incidence of cerebral hemorrhage, (2) the incidence of hypertrophy of the heart, and (3) the incidence and degree of arterial hypertension] study of these series demonstrated that the frequency of arterial hypertension is considerably lower in patients with severe hepatic disease than in patients without liver disease.

The hypothesis has been advanced that severely impaired liver function is able to prevent the development of arterial hypertension, or can eliminate already existing hypertension.

Sumario Español

Una comparación con relación a la incidencia de la hipertensión arterial se ha hecho entre una serie de autopsias consistiendo de 102 mujeres que murieron de hepatitis crónica (atrofia amarilla subcrónica del hígado) y una serie control de pacientes a quienes se les practicó autopsia que no tenian enfermedad hepática. Por medio de tres criterios para la presión arterial [(1) la incidencia de hemorragia cerebral, (2) la incidencia de hipertrofia del corazón y (3) la incidencia y el grado de hipertensión arterial] el estudio de estas series demostró que la frecuencia de hipertensión arterial es considerablemente más baja en pacientes con enfermedad severa hepática que en los pacientes sin enfermedad hepática.

La hipotesis se ha propuesto que la función hepática severamente deteriorada es capaz de evitar el desarrollo de hipertensión arterial o que puede eliminar la hipertensión ya existente.

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Prevention of Systemic Arterial Embolism in Chronic Rheumatic Heart Disease by Means of Protracted Anticoagulant Therapy

By JOHN C. WOOD, M.D., AND HADLEY L. CONN, JR. M.D.

Seven clinic outpatients with mitral stenosis and auricular fibrillation complicated by systemic embolism have been maintained on Dicumarol for periods of 20 to 48 months. None has had a recognized embolism while on therapy. Dicumarol administration has been interrupted in each case for periods of six days to four months. Three additional systemic embolic episodes in two individuals occurred during this interval. Hemorrhagic manifestations have occurred on three occasions. The study suggests that: (a) protracted Dicumarol therapy is an effective means of preventing recurrent embolism in individuals with chronic rheumatic heart disease; (b) it is applicable to the average clinic outpatient.

SYSTEMIC arterial embolism is a recognized hazard in chronic rheumatic heart disease. Except for bacterial endocarditis which is not considered in this paper, it most commonly results from mural thrombosis complicating mitral stenosis with auricular fibrillation.

Following the successful employment of anticoagulants in the acute problems of thromboembolism, it was logical that their use should be extended to those individuals under chronic threat of embolism. The major question arising from this transition was whether anticoagulant drugs could be administered to the ambulatory patient without prohibitive risk of hemorrhage. This led Foley and Wright to select only "intelligent, co-operative private patients" in their exploratory work with outpatient treatment.[1, 2] Since then a number of observations have been published, varying from casual references and isolated case reports to the extensive accumulated data of Cosgriff and Wright.[3 to 12] The over-all experience suggests that prolonged anticoagulant therapy provides significant protection against recurrent embolism within the limits of an acceptable therapeutic risk.

This report presents our experience with the use of long-term Dicumarol* therapy as prophylaxis against recurrent systemic arterial embolism in patients with chronic rheumatic valvular disease who refused, or were rejected for, mitral valve surgery.

Case Material

The series includes all individuals with rheumatic valvular disease followed in our Cardiac Clinic who have received Dicumarol over long periods of time to prevent recurrent arterial embolism (table 1). It consists of four females and three males with an age range at the time of initiation of therapy from 35 to 60 years. All have predominant mitral stenosis with chronic auricular fibrillation. Two patients (cases 2 and 6) have a minor degree of aortic valvular involvement. Cardiac classifications (American Heart Association) have ranged from II-B to IV-D. All patients have been placed on a restricted sodium intake and are receiving digitalis. Five have required mercurial diuretics. In each of the seven patients, anticoagulant therapy was instituted after one or more systemic embolic episodes.† Altogether 10 such episodes preceded treatment with Dicumarol (table 1).

The clinical diagnosis of arterial embolism involving an extremity (seven episodes) or the brain (one episode) was clearly warranted in each instance. Surgical confirmation was obtained in three patients at the time of embolectomy (cases 4 and 6) or ampu-

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Dr. Wood is a Trainee of the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

Dr. Conn is a Research Fellow of the American Heart Association.

* 3,3′-methylenebis-(4 hydroxycoumarin).

† Emboli to different sites occurring at the same time are considered as a single episode.

TABLE 1.—*Case Material*

Case No.	Age	Sex	Diagnosis	Embolic Episodes Before Treatment§
1	51	F	* RHD † M.S., M.I., A.F. ‡ II-B	(1) Abdomen (2) Right and left legs (3) Right femoral and left popliteal arteries
2	51	M	RHD M.S., A.I., A.F. III-C to II-B	(1) Aortic bifurcation Kidney
3	58	F	RHD M.S., A.F. II-B to III-C	(1) Brachial artery
4	58	M	RHD M.S., A.F. II-B to III-C	(1) Spleen (2) Right external iliac artery
5	35	F	RHD M.S., M.I., A.F. III-C	(1) Cerebrum
6	60	M	RHD M.S., M.I., A.S., A.F. II-C	(1) Left iliac artery Abdomen Flank
7	44	F	RHD M.S., A.F. IV-D to III-C	(1) Left popliteal artery
Total	7 patients			10 embolic episodes

* Chronic inactive rheumatic heart disease.

† M.S. = Mitral Stenosis; M.I. = Mitral Insufficiency; A.S. = Aortic Stenosis; A.I. = Aortic Insufficiency; A.F. = Auricular Fibrillation.

‡ American Heart Association Classification.

§ Emboli to different sites occurring at the same time are considered as a single episode.

tation (case 2). An otherwise unexplained episode of severe abdominal pain led to a presumptive diagnosis of visceral embolism in one individual (case 1). In one instance (case 4) left upper quadrant pain and tenderness accompanied by a transient friction rub indicated splenic embolism. Acute abdominal and flank pain accompanying sudden occlusion of the left iliac artery suggested associated visceral involvement in another instance (case 6). In one patient (case 2) renal embolism was thought likely because of a history of "mahogany" colored urine in conjunction with leg symptoms subsequently shown to be the result of a saddle embolus.

METHOD OF MANAGEMENT AND RESULTS

Our method of administration and control of anticoagulants has been similar to the practice of others.[1, 2, 6, 12] In six cases, therapy was begun immediately after an embolic episode; initially each received heparin until adequate prolongation of the prothrombin time was achieved with Dicumarol. In the seventh patient (case 5) Dicumarol was first given approximately one year after a cerebral embolism. All our patients were hospitalized during initial Dicumarol administration and stabilization. During the early outpatient period, prothrombin time determinations were done at four- to seven-day intervals. The time interval was subsequently increased to two weeks except for transient periods when hemorrhagic phenomena or erratic variations of the prothrombin times occurred. In one patient (case 5), a hospital employee under frequent clinical ob-

servation, intervals up to three weeks have been permitted.

Each individual has been thoroughly instructed in the potential danger of anticoagulants, and in the need for prompt action in the event of hemorrhagic manifestations. All have been encouraged to contact their clinic physicians by phone should any question as to therapy arise.

The average daily maintenance dose of Dicumarol has varied between 100 and 175 mg. in one patient, between 50 and 75 mg. in four, and between 25 and 50 mg. in the remaining two (table 2). At each clinic visit, a tentative Dicumarol dosage schedule has been arranged. This schedule has been confirmed, or altered if necessary, in a regular telephone report later the same day after the report of the prothrombin time was received.

This program has succeeded in maintaining prothrombin levels between 20 per cent and 35 per cent in most of the patients most of the time. In no case have we been able to avoid completely deviations above or below these limits. Variations of the prothrombin time beyond the desired range have been infrequent in four cases, occasional in two, and frequent in one. These results arbitrarily have been categorized as "good," "fair," and "poor control," respectively (table 2). Two patients (cases 2 and 3) are considered "good" by these criteria in spite of single episodes of bleeding.

Three individuals have had isolated instances of Dicumarol overdosage with hemorrhagic phenomena (table 2). These have consisted of microscopic hematuria and numerous leg petechiae in one (case 2); gross hematuria, skin ecchymoses and protracted bleeding following a minor laceration in a second (case 3); and gross hematuria, epistaxis, buccal ecchymoses and asymptomatic small retinal hemorrhages in the third (case 6). In two of the three instances, the patients had failed to keep their preceding clinic appointments. The intravenous administration of vitamin K_1 emulsion resulted in prompt cessation of bleeding and a return of the prothrombin time to safe levels within 24 hours in each instance. Blood transfusions were not required.

TABLE 2.—*Control of Dicumarol Therapy*

Case	Average Daily Dicumarol Maintenance Dose	Quality of Prothrombin Time Control*	Hemorrhagic Episodes Complicating Dicumarol Therapy†
	mg.		
1	25–50	Good	0
2	50–75	Good	1
3	50–75	Good	1
4	25–50	Good	0
5	100–175	Fair	0
6	50–75	Poor	1
7	50–75	Fair	0‡

* Good—Infrequent deviations beyond 20–35% of normal prothrombin activity.
Fair—Occasional deviations beyond 20–35% of normal prothrombin activity.
Poor—Frequent deviations beyond 20–35% of normal prothrombin activity.

† Case 2. Microscopic hematuria and numerous leg petechiae.
Case 3. Gross hematuria, ecchymoses and prolonged bleeding following a minor laceration.
Case 6. Gross hematuria, epistaxis, buccal ecchymoses and asymptomatic small retinal hemorrhages.

‡ Case 7. Retroperitoneal hemorrhage in hospital when heparin was given after a lumbar sympathetic nerve block.

In addition, occasional small ecchymosis have occurred in two patients (cases 1 and 3) and slight gum bleeding associated with pyorrhea has been noted in another (case 4) when the prothrombin time was in the desired range.

While hospitalized, and prior to Dicumarol therapy, one patient (case 7) experienced retroperitoneal hemorrhage when heparin was given shortly after a paravertebral sympathetic nerve block. The incompatability of lumbar sympathetic nerve block and anticoagulant administration has been stressed by others.[13, 14]

None of our patients has had a clinically apparent embolism while taking Dicumarol. Treatment has been given to individuals for periods varying from 20 to 48 months, or a combined total for all patients of 214 treatment months (table 3). Six patients are still being maintained on Dicumarol. In the seventh (case 7), Dicumarol was stopped after 15 months and a mitral commissurotomy was performed. At operation, no auricular

TABLE 3.—*Periods of Dicumarol Administration and Withdrawal with Respect to Embolic Episodes*

Case	Duration of Dicumarol Therapy	Embolic Episodes during Dicumarol Therapy	Duration of Periods of Dicumarol Withdrawal	Embolic Episodes during Periods of Dicumarol Withdrawal
	mos.			
1	29	0	7 days	0
2	26	0	14 days	0*
3	29	0	12 days	(1) Right popliteal artery
4	1st 17	0	4 mos.	(1) Cerebrum
	2nd 17			(2) Left popliteal artery; abdomen
	Total 34			
5	48	0	6 days	0
6	28	0	37 days	0†
7	20	0	12 days	0
Total 7.....	214	0	7 mos.	3 embolic episodes

* Pulmonary embolism occurred in hospital when heparin therapy was withdrawn to permit supracondylar amputation.

† No embolic episodes since Dicumarol therapy stopped seven months ago, five months following mitral commissurotomy.

thrombus was found. Three days after surgery, anticoagulant therapy was resumed and continued for five months. It was then stopped because congestive failure had improved. This patient has not had an embolism since then, a period of seven months.

In all seven patients anticoagulant administration has been interrupted for periods varying from a few days to approximately four months, or a combined total for all patients of seven months (table 3). Except in one instance (case 4), this was done in anticipation of a dental extraction or a surgical procedure. Three additional embolic episodes in two individuals occurred during such an interval (table 3). One patient (case 3) had sudden occlusion of the right popliteal artery five days after Dicumarol was stopped and vitamin K_1 administered to permit cholecystectomy. One individual (case 4) was taken off Dicumarol by his family physician after an initial 17-month period of successful prophylaxis. Three months later he experienced left hemiparesis followed in one month by abrupt occlusion of the left popliteal artery concomitant with acute abdominal pain. At this time we placed him on a regular dose of Dicumarol once more. He has continued to take it to the present time, a period of 17 months, and has had no further embolism. A third patient was placed on heparin, as a preliminary to Dicumarol therapy, following a saddle embolus. Progressive ischemic necrosis of the left leg made necessary a supracondylar amputation. Heparin was withdrawn to permit surgery, shortly following which a probable pulmonary embolism occurred.

A total of 13 systemic embolic episodes, therefore, has occurred in the seven patients while not on Dicumarol during the combined pretreatment and withdrawal periods. In addition, one pulmonary embolism occurred when heparin administration was interrupted. In contrast, there has been no instance of embolism during the period of anticoagulant administration.

DISCUSSION

The reported frequency of embolism in mitral stenosis with auricular fibrillation varies in different reports, possibly according to the duration of observation and manner of patient selection. Parkinson and Campbell[15] and Viko and co-workers[16] noted an incidence of 4 per cent and 8 per cent, respectively, without distinguishing between involvement of the pulmonary and systemic arterial sides of the circulation. However, it has been estimated that 20 per cent of these patients die from thromboembolism, the majority showing systemic embolic infarctions.[7] Of patients selected by Janton and his associates for mitral

valve surgery, 22 per cent had experienced systemic arterial embolism.[17] An incidence of 9 per cent was noted in another surgical series[18] in which it was not specified whether all involved the systemic circulation. A recent clinicopathologic study revealed evidence of systemic arterial embolism, most of which had been manifest clinically, in 18 per cent of the cases.[19] In a postmortem analysis of 164 cases of rheumatic heart disease where cardiac disability was severe and responsible for death, systemic or pulmonary infarcts were found in 45 per cent.[20] It has been emphasized that visceral embolism found at autopsy had often been unsuspected clinically.[8, 20] Although an occasional individual may live for years following an embolism without a recurrence,[1, 8] repeated episodes are to be expected in the majority of patients, commonly following one another within six months.[8]

The problem of prevention of recurrent embolism in this condition has not been completely solved. The main preventive therapeutic procedures which have been tried clinically include conversion to sinus rhythm with quinidine, prolonged anticoagulant regimens, left auricular appendage ligation or resection, and mitral commissurotomy.

A difference of opinion exists as to the danger of embolism associated with conversion of auricular fibrillation to normal sinus rhythm with quinidine. However, it is generally felt that the risk of quinidine administration is increased and the maintenance of sinus rhythm difficult in the presence of rheumatic heart disease and long-standing auricular fibrillation, especially when accompanied by congestive heart failure.[3, 8, 15, 16, 21] Therefore, the use of quinidine in this situation has not gained wide acceptance. Today, in the presence of mitral stenosis, surgery limited to resecting the left auricular appendage seems ill-advised. It has been demonstrated that mural thrombi in chronic rheumatic heart disease are situated in regions other than left auricular appendage in more than 50 per cent of the cases.[8, 22, 23, 24] Secondly, left auricular appendectomy or ligation would complicate, if not prevent, a subsequent attempt to open the mitral valve.

Mitral commissurotomy is probably the method of choice in handling this problem at the present time,[17] although embolism in the operative or immediate postoperative period is a hazard.[17, 18, 19, 25] There will remain some patients who are not suitable for, or who refuse, surgery and a group with recurrence after mitral valvulotomy. In these individuals long-term anticoagulant therapy seems indicated. The complete freedom from embolism in our patients during a total treatment period of over 200 patient months is in sharp contrast to the pretreatment period and to the occurrence of three additional systemic emboli during the total period of seven patient months when Dicumarol was withdrawn. Our experience, combined with previous observations, has led us to have the following point of view concerning the use of long-term Dicumarol therapy in patients with rheumatic mitral valvular disease:

(1) Absolute protection against embolism is not necessarily to be expected. Insurance against dislodgement of preformed mural thrombi cannot be provided. It is difficult, if not impossible, to maintain a therapeutically effective prothrombin time in all patients at all times.

(2) Because of the close individual attention required for safe anticoagulant administration and the fact that many patients with mitral stenosis and auricular fibrillation do not experience clinically apparent embolism, we have limited Dicumarol therapy to those persons with preceding embolic manifestations. Possibly a subgroup of these patients who (a) are in the older age range, (b) have a severe degree of mitral stenosis, and (c) have congestive failure might be selected as suitable for long-term treatment. Further study of this problem seems indicated.

(3) Because of the danger of local hemorrhage, it is probably good judgment to avoid using anticoagulants immediately following a cerebral embolism.[26]

(4) Dicumarol should not be administered to ambulatory patients in the absence of adequate laboratory and clinical control. The latter demands alertness of the physician as well as cooperation on the part of the patient. Careful education of the patient concerning

the purpose and toxicity of Dicumarol is important. It makes practicable, for the average clinic outpatient, an anticoagulant program where the period between laboratory checks is fixed on what must be conceded to be an arbitrary basis. Unpredictable variations in the effect of Dicumarol are not entirely eliminated by weekly prothrombin time determinations.

(5) Provided the requirements of (4) are met, serious hemorrhage rarely should occur although occasional hemorrhagic manifestations are to be anticipated. These generally can be controlled readily with vitamin K_1 which is superior to water soluble analogs.[27, 28]

(6) Once instituted, unless the basic situation is altered, as by mitral commissurotomy, there is no way of selecting a point of safe withdrawal. Therefore, therapy probably should be continued indefinitely in most patients. Although not substantiated, the possibility exists that a temporary state of relative hypercoagulability may follow withdrawal of anticoagulants.

(7) Recognizing the foregoing limitations, protracted Dicumarol therapy appears to be a reasonably effective means of preventing recurrent embolism.

In the use of Dicumarol on an outpatient basis, we have been inclined to err in the direction of inadequate prolongation of the prothrombin time to reduce the risk of hemorrhage. Some reassurance in this policy is gained through our own favorable results and the empiric observations of others[10, 29] that protection appears to be afforded with less prothrombin suppression than the generally accepted range of 10 or 15 per cent to 30 per cent.[1, 2, 6, 12]

Summary

Seven clinic outpatients with mitral stenosis and chronic auricular fibrillation complicated by previous systemic arterial embolism have been maintained on anticoagulant therapy for periods of 20 to 48 months. No patient has had a recognized embolism while on therapy. Two individuals had further systemic embolism during periods of temporary Dicumarol withdrawal. An additional patient experienced pulmonary infarction when heparin administration was interrupted. Hemorrhagic phenomena of a degree sufficient to necessitate therapy with vitamin K_1 have occurred on three occasions.

This study suggests that long-term Dicumarol administration is an effective means of preventing recurrent embolism in individuals with chronic rheumatic heart disease and that it is applicable to the average clinic outpatient.

Addendum

Since the writing of this paper, one patient (case 4) has had an episode of mental confusion and apparent slight right-sided weakness which cleared without residuum within 24 hours. This occurred when the prothrombin value was 32 per cent. It is felt reasonable to consider this as an embolic episode.

Sumario Español

Siete pacientes ambulatorios con estenosis mitral y fibrilación auricular crónica complicada con previos émbolos arteriales sistémicos han sido mantenidos en terapia anticoagulante por períodos de 20 a 48 meses. Ningún paciente ha tenido un embolismo reconocido durante la terapia. Dos individuos tuvieron embolismos reconocidos durante períodos de descontinuación temporera del Dicumarol. Un paciente adicional experimentó un infarto pulmonar cuando la administración de heparina se interrumpió. Fenomenos hemorrágicos de suficiente grado para requerir tratamiento con vitamina K_1 ocurrieron en tres ocasiones.

Este estudio sugiere que la administración por largo término de Dicumarol es un medio efectivo para la prevención del embolismo recurrente en individuos con enfermedad reumática cardíaca crónica y que es aplicable al paciente promedio ambulatorio.

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Bacterial Endocarditis and Mural Thrombi in the Heart

By JACQUES B. WALLACH, M.D., MACELLIS GLASS, B.A., LESLIE LUKASH, M.D., AND ALFRED A. ANGRIST, M.D.

The infrequent occurrence of mural thrombi in the chambers of the heart is noted. The relevant literature is reviewed. The findings in eighty-two cases of bacterial endocarditis superimposed on rheumatic heart disease and in 47 examples of bacterial endocarditis without underlying rheumatic valvulitis are reported. These findings may reflect the infrequency of auricular fibrillation and of severe mitral stenosis in cases of bacterial endocarditis. The results further substantiate the origin of emboli from the valvular vegetations, bacterial or nonbacterial, rather than from the cardiac chambers, and this correlates with the bland character of most of the infarcts.

EMBOLIC phenomena occur with such frequency in the course of bacterial endocarditis as to constitute a cardinal diagnostic feature of this disease. However, it has been noted that the resultant infarcts are less often septic than would be expected if the emboli originated from the infected valvular vegetations.[1] A previous study of this apparent paradox showed that it is the nonbacterial thrombotic vegetation that is a frequent source of these emboli in patients with rheumatic heart disease with or without superimposed bacterial endocarditis.[2] An incidental feature of this analysis, further substantiating the above findings, was the relative rarity of mural thrombi as the origin of such bland emboli in the cases of bacterial endocarditis.

Another report also indicated the relative infrequency of severe mitral stenosis with bacterial endocarditis as well as the greater rarity of auricular fibrillation in patients with bacterial endocarditis.[3] The role of each of these factors in the formation of mural thrombi in the left auricle has been discussed previously.[4]

A perusal of the recent literature discloses few references dealing specifically with this subject. Garvin[5] in a study of mural thrombi in the heart found only 1 instance of mural thrombus in 30 cases of subacute bacterial endocarditis (3.3 per cent) and none in 13 cases of acute bacterial endocarditis. He concluded that this complication was distinctly uncommon in these diseases but offered no explanation. The standard textbooks do not mention this association.[6]

From the Department of Pathology, Queens General Hospital, Jamaica, N. Y.

MATERIAL AND METHODS

In order to study this problem with a large series of uniformly examined cases, 8676 consecutive autopsies performed at the Queens General Hospital from 1936 to 1950 inclusive were reviewed. The hearts of 509 (5.9 per cent) of the cases thus studied were classified as showing rheumatic heart disease since they fulfilled the following criteria[7]: (1) fusion and retraction of the mitral or tricuspid valves; (2) fusion and shortening of the chordae tendineae; (3) noncalcific fusion of the aortic valve; (4) any fusion, including calcific changes, of the aortic valve when it was associated with definite rheumatic mitral valve involvement; (5) active rheumatic heart disease with Aschoff bodies or characteristic verrucae; (6) bacterial endocarditis of the mitral or aortic valves with some evident previous distortion, but the exact estimation of the severity of rheumatic damage being difficult.

Cases showing the following changes were excluded from this study: (1) slight mitral changes (for example, tongue-like extensions of the valve cusps), or distortion which did not fulfill the criteria stated above (points 1 and 2); (2) slight aortic stenosis with or without slight mitral involvement; (3) calcific aortic stenosis with or without slight mitral changes; (4) calcification of the valve rings alone. Thus 103 cases of calcific aortic stenosis and 72 cases of doubtful origin were excluded from this study.

In the group of rheumatic hearts, bacterial endocarditis was present in 82 (16.1 per cent); in five the endocarditis was healed. These patients were compared with 47 patients with bacterial endocardi-

tis in whom the hearts did not meet the criteria for rheumatic heart disease described above. In each case, the occurrence of mural thrombi in the chambers of the heart, the presence of auricular fibrillation and the severity of the mitral stenosis were noted. When the cardiac rhythm was abnormal, the time of onset relative to the beginning of the valvular infection was ascertained.

The present paper deals with the relationship of mural thrombi to bacterial endocarditis.

Results

Mural thrombi occurred in the cardiac chambers in 8 of the 82 cases (9.3 per cent) of bacterial endocarditis superimposed on rheumatic heart disease. Four of these had regular rhythm; two had auricular fibrillation terminally. Only two patients had preceding chronic auricular fibrillation and in one of these the endocarditis was acute. Mural thrombi were noted in 2 of the 47 cases of bacterial endocarditis which did not fulfill the criteria for underlying rheumatic heart disease. Both of these had acute terminal endocarditis, one with regular rhythm and one with preceding auricular fibrillation.

In contrast to these findings, mural thrombi were found in 137 (27 per cent) of the total 509 cases of rheumatic heart disease. One hundred twenty-nine of these cases (30 per cent) occurred in the 427 cases of rheumatic heart disease without bacterial endocarditis.

Of the 72 cases with valvular lesions of doubtful origin, thrombi were present in the heart in seven cases. Five of these were associated with myocardial infarction; in the other two cases the thrombus was in the right auricle or right appendage. The rhythm was regular in all but one case which had auricular fibrillation associated with fresh myocardial infarction.

Comment

Although there are not sufficient cases for statistical evaluation, the data do not suggest that auricular fibrillation is responsible for the mural thrombi in these cases of bacterial endocarditis. The results of the present study indicate the relative rarity of mural thrombi in the heart in cases of bacterial endocarditis with underlying rheumatic heart disease (approximately 10 per cent). This is in contrast to that for the total cases of rheumatic heart disease (27 per cent). These findings may well be a reflection of the demonstrated infrequency in cases of bacterial endocarditis of auricular fibrillation and of severe mitral stenosis.[3] The role of these two factors in the formation of left auricular mural thrombi has been discussed previously.[4]

These findings further substantiate the origin of emboli from the valvular vegetations, rather than from the cardiac chambers despite the bland character of most of the infarcts. The data indicating the source of these emboli from nonbacterial thrombotic vegetations on the valves has been presented previously.[2]

Summary and Conclusions

The relative infrequency of mural thrombi in the chambers of the heart is reported in 82 cases of bacterial endocarditis superimposed on rheumatic heart disease and in 47 cases of bacterial endocarditis without underlying rheumatic heart disease.

The relevant literature is reviewed and the possible explanation of this finding is presented on the basis of infrequency of auricular fibrillation and of severe mitral stenosis in cases of bacterial endocarditis (both related to the formation of mural thrombi).

Sumario Español

La rareza relativa de trombos murales en las cámaras del corazón se informa en 82 casos de endocarditis bacterial sobrepuesta en enfermedad reumática del corazón y en 47 casos de endocarditis bacterial sin enfermedad cardíaca reumática subyacente.

La literatura pertinente se revisa y la posible explicación de este hallazgo se presenta a base de la rareza de la fibrilación auricular y de la estenosis mitral severa en los casos de endocarditis bacterial (ambos relacionados a la formación de trombos murales).

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Observations on the Interatrial Pressure Gradients in Man

By A. B. SHAFFER, M.D., E. N. SILBER, M.D., AND L. N. KATZ. M.D.

It was possible to calculate pressure gradients across the interatrial septum in several cases of congenital heart disease. Gradients in cases of interatrial septal defect are similar to those found in animals with artificially produced defects. The data are used to form a rounded picture of the hemodynamics of interatrial septal defect. In pulmonic stenosis with interatrial communication, reversal of the usual left-to-right gradient may occur only during atrial systole. Under these circumstances it is often possible to distinguish a patent foramen ovale with competent valve from an interatrial septal defect.

ATRIAL hemodynamics have been extensively studied in animals[1–7] with or without interatrial communications. Despite the widespread use of right heart catheterization, there is still a paucity of such information in man.

During routine right heart catheterization of several patients with congenital heart disease, passage of the catheter through interatrial communications made it possible to record pressure pulses from both atria. An analysis of these curves, insofar as it provides information on atrial hemodynamics in man, forms the basis of this report.

METHODS

The data consisted of atrial pressure pulses from 14 cases with congenital interatrial communications. Seven of these sets of curves were unsuitable for detailed analysis because of artefacts or large respiratory variations. However, the data from these discarded cases lend themselves to the same interpretation as the seven analyzed in detail.

The atrial pressure curves were recorded from each atrium in quick succession, using the Sanborn capacitance manometer (fig. 1). A simultaneously recorded electrocardiogram (lead II) served as a time reference. The patients were supine and breathing quietly. The zero level was 5 cm. dorsad to the angle of Louis. Blood samples were obtained in each case from both atria. The presence and magnitude of right-to-left shunting of blood in the atria were determined by comparing the oxygen content of left atrial or systemic arterial blood with that of pulmonary venous blood. Where the latter was not available, 95 per cent saturation was assumed. Left-to-right shunting of blood in the atria was indicated by the high oxygen content of right atrial blood relative to caval blood. The pressure pulses and blood samples from other chambers and vessels were used to complete the hemodynamic picture and to arrive at a final diagnosis.

The pressure differences between the left and right atrial curves during several heart cycles were determined for each 0.04 second, using the summit of the QRS as a zero time reference point. In each case, the cycle lengths of the atrial curves selected were identical and were, as far as could be determined, from the same phase of the respiratory cycle. The results were plotted as graphs representing the cyclic interatrial pressure gradients. Examples of these are shown in figures 2 to 8. The general similarity of the graphs from cases of interatrial septal defect indicates that there is validity to this analysis despite the errors inherent in pressure recording through a catheter due to movement of the heart[1] or to the variable position of the catheter opening relative to the direction of blood flow.[8]

The atrial pressure pulses were used as recorded and have not been expressed as effective atrial pressures by subtraction of the simultaneous intrathoracic pressure near the respective atria.[2, 9] It is unlikely that a significant difference between the intrathoracic pressures around each atrium exists at any instant[3, 4] although reports to the contrary have appeared.[10, 11] The latter possibility, and the difficulty of matching right and left atrial pressure pulses from exactly the same phase of the respiratory cycle, mean that the phasic pressure differences recorded are not likely to be absolutely correct. However, in patients such as ours, where breathing was slow and shallow, respiratory pressure variations were slight and the graphs are considered to be accurate enough for study.

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

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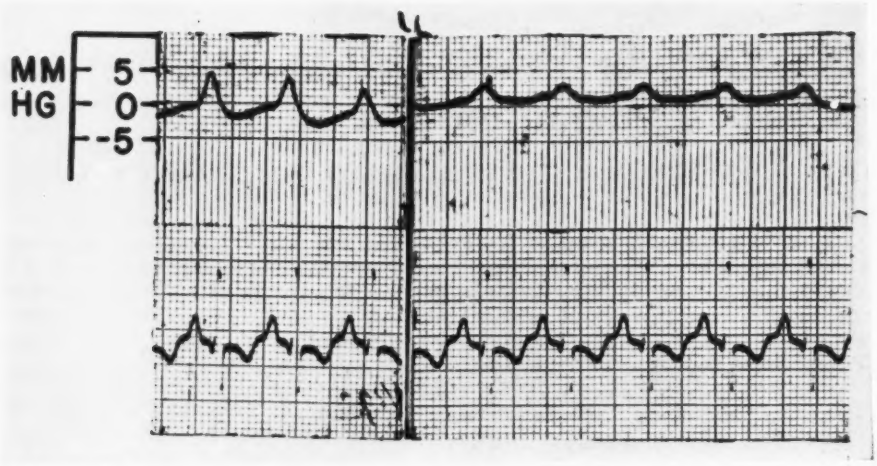

FIG. 1. Atrial pressure pulses from a case of valvular pulmonic stenosis with a patent foramen ovale. *Left:* right atrial pressure pulse. *Right:* left atrial pressure pulse. Electrocardiogram: lead II.

RESULTS

1. *Interatrial Septal Defects, Uncomplicated or with Pulmonary Hypertension*

The first three cases (figs. 2 to 4) had normal or almost normal pulmonary pressures, large left-to-right shunts and very small right-to-left shunts. The fourth (fig. 5) had a high pulmonary arterial pressure and the left-to-right shunt was less marked.

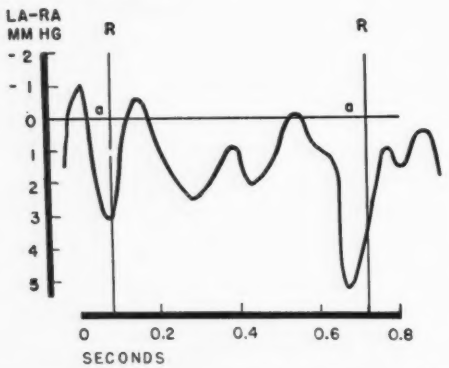

FIG. 2. Cyclic pressure gradient across the interatrial septum in a case of uncomplicated interatrial septal defect (left atrial pressure–right atrial pressure in mm. Hg). A left-to-right pressure gradient is present when the graph is below the zero line, and the gradient is reversed when the graph is above the zero line. R = summit of the QRS of the electrocardiogram; a = period of atrial systole.

In all four cases the pressure gradient through each cardiac cycle is by and large from left to right, with the maximum gradient during atrial systole. There is a more sustained but less marked peak during ventricular systole, the period of rapid atrial inflow,[12] and this reaches its maximum during the "v" wave of the atrial pulse. The left-to-right pressure gradient drops when the A-V valves open and remains small until the next atrial systole. The time of opening of the A-V valves could be estimated within about 0.02 second. This occurred at 0.48 second in figure 2, at 0.48 and 1.20 seconds in figure 3 (best seen here on account of the slower rate), 0.8 second in figure 4 and 0.56 second in figure 5. The pressure gradient is least either early in atrial systole or just after it. Each graph, except that of figure 4 where the gradient reaches zero, shows reversal of the gradient at one or both of these times. The blood oxygen data of each case

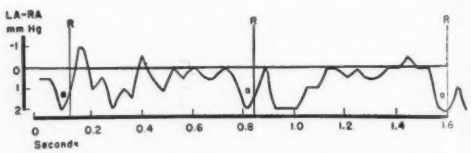

FIG. 3. Cyclic pressure gradient across the interatrial septum in a case of uncomplicated interatrial septal defect. Conventions as in figure 2.

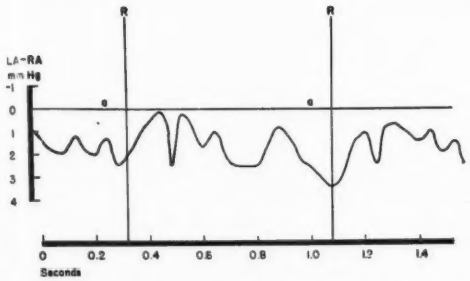

FIG. 4. Cyclic pressure gradient across the interatrial septum in a case of interatrial septal defect with mild pulmonary arterial hypertension. Conventions as in figure 2.

indicated a small right-to-left shunt. Thus, despite the fact that the left atrial mean pressure exceeded the right, there was evidence of small transient reversals both of the gradient and of the flow through the defect in all cases. The inadequacy of mean pressures in the study of the intimate hemodynamics of the atria is obvious,[1, 2] and is again stressed here.

The present graphs do not differ significantly from those of dogs with artificial interatrial septal defects.[2, 5] The drop in left-to-right gradient on opening of the A-V valves and the transient reversal of this gradient before or after atrial systole are seen in both human and animal curves. However, in animal experiments the left-to-right gradient is most often described as smallest in the middle or at the end of atrial systole rather than at the beginning and end. This difference between man and the dog is more apparent than real and depends on the conventions used in identifying the time of events in this part of the cycle. In all our cases where it could be clearly defined, and contrary to reports by other investigators,[1, 13] the right atrial "a" waves begin 0.02 to 0.03 second before the left, and reach their peak that much sooner. This is also observed in curves obtained from dogs[2, 3] and would be expected to reduce or reverse the left-to-right gradient at the beginning of atrial systole. The manner of spread of the impulse from the sinus node explains the asynchrony between the left and right atrial contraction.

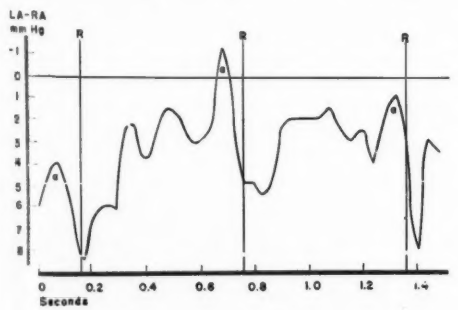

FIG. 5. Cyclic pressure gradient across the interatrial septum in a case of interatrial septal defect with moderately severe pulmonary arterial hypertension. Conventions as in figure 2.

2. *Valvular Pulmonic Stenosis Associated with Interatrial Communication*

The left-to-right gradient, which is accentuated during atrial systole when interatrial septal defect is the significant lesion, is by contrast markedly reversed in figure 6 except at the very end of atrial systole. During the rest of the cycle there is a left-to-right pressure gradient. Because of the rapid heart rate in this case, the effect of opening of the A-V valves is obscured by the simultaneous occurrence of atrial systole. The right-to-left shunt in this case was sufficient to account for a thirteen per cent difference between the oxygen contents of the pulmonary venous and brachial arterial blood samples, but there was no evidence of a left-to-right shunt on careful sampling of the right atrium, despite the marked and prolonged left-to-right gradient. (The mean gradient was left to right, but the only shunt was right to left.) It is deduced from the latter fact that the interatrial communication through which the catheter passed is a patent foramen ovale.

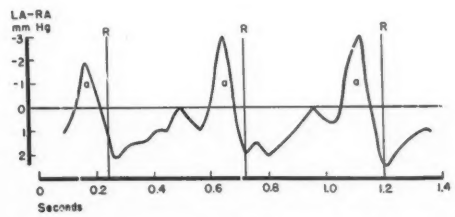

FIG. 6. Cyclic pressure gradient across the interatrial septum in a case of severe valvular pulmonic stenosis with a patent foramen ovale. Conventions as in figure 2.

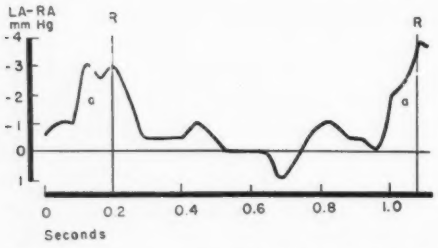

FIG. 7. Cyclic pressure gradient across the interatrial septum in a case of severe valvular pulmonic stenosis with an interatrial communication in early right heart failure. Conventions as in figure 2.

Figure 7 shows the interatrial pressure gradient in a similar case. There was very severe valvular pulmonic stenosis with early right heart failure as evidenced by an elevated right ventricular end-diastolic pressure. In this case, the right atrial pressure is higher than the left through most of the cycle, and, like the previous case, it is most marked during atrial systole. Only for a short time at the moment of the A-V valve opening (0.68 second) when, under the circumstances, right ventricular inflow would be most free, is there a left-to-right gradient. This graph indicates that the shunt, if any, is right to left during most of the cycle. In this case, the shunt was large enough to cause overt cyanosis; evidence of a left-to-right shunt was completely lacking.

3. *Interventricular Septal Defect and Patent Foramen Ovale*

Figure 8 shows the interatrial pressure gradient in a case of interventricular septal defect and patent foramen ovale associated with a moderate pulmonary hypertension. The left-to-right atrial pressure gradient is very marked and reversal occurs to a slight degree only at the end of atrial systole in two of the three heart cycles shown. The left-to-right gradient is augmented during the period of rapid atrial filling, and then rises sharply again during atrial systole. This graph may be considered as an exaggeration of the graphs of interatrial septal defect shown before. Despite the marked left-to-right gradient, no shunt was evident in either direction. Thus, the interatrial communication was a patent foramen ovale.

DISCUSSION

The present observation that mean pressure is higher in the left atrium than in the right in patients with uncomplicated interatrial septal defect is in agreement with others.[14-16] This is also true in normal dogs.[1, 3, 17, 18] The creation of an interatrial septal defect moderate in size in the dog does not alter this relationship,[2, 5, 18] although the gradient is lessened somewhat because of an increase in right atrial pressure.[5] Thus, it would seem reasonable to assume that left atrial pressure usually exceeds right atrial pressure in normal man.

A number of mechanisms may account for the pressure differences between the atria. These include:

1. The different pressure-volume characteristics of the two atria, suggested on anatomic grounds in man, both with and without interatrial septal defects,[19, 20] and proved directly in dogs[21] and to some extent in man.[22, 23] Both in the dog and in man, the left atrium has a smaller cavity and a thicker wall than the right.

2. The smaller capacity of the venous system draining into the left atrium than into the right[1, 8, 15] so that each increment of volume causes a greater increment of pressure in the pulmonary veins and left atrium than in the cavae and right atrium.

3. The greater extent and greater peripheral resistance of the systemic circuit as compared with the pulmonary circuit may mean that right ventricular contraction exerts a greater *vis a tergo* effect on venous return than does left ventricular contraction.[8]

4. Variations in the movement of the A-V junction on the two sides may result in higher pressure in the left atrium than in the right during ventricular systole.[15]

5. The smaller area of the mitral orifice compared to the tricuspid, as well as the thicker wall and smaller cavity of the left ventricle compared to the right, have been considered as the basis of a greater resistance to inflow into the left ventricle than into the right.[19, 24]

This last point led to the suggestion that the left-to-right gradient across the interatrial septum in uncomplicated interatrial septal defect should be small before the A-V valves

open and should increase afterwards.[19] We have observed exactly the reverse. Since in the normal human heart the blood flow is equal through the mitral and tricuspid valves, it is possible, but unproved, that the pressure is higher in the left atrium than in the right during ventricular filling. However, in the presence of an interatrial septal defect, the unequal ventricular inflows may, in part, nullify this difference through some rise in right ventricular filling pressure, and there is some evidence for this in man[25] and in the dog.[5] Certainly, the present data in cases of interatrial septal defect show that filling pressures in the two ventricles approach each other. The pressures in both atria fall when the A-V valves open but the fall is greater in the left atrium. This was found in such curves from dogs[1] but was not marked in another study on man.[20]

It is generally agreed that the minute flow of blood in uncomplicated interatrial septal defect may be considered in the following terms: (1) There is a large left-to-right flow of blood through the defect.[14-16, 18, 26, 27] Although the cephalad position of the left atrium with respect to the right has not been generally accepted as a factor contributing to the left to right shunt,[28] there is some support for the idea.[29] (2) The minute flow through one atrium is the same as that of the other and both vary directly with the size of the shunt. (3) Systemic minute-flow, and with it venous return to the right atrium, is often reduced.[3, 19] (4) Despite the greatly increased flow through all chambers except the left ventricle, there is no demonstrable deviation in pressure from the normal except for the possible rise in right ventricular end-diastolic pressure.[25]

At present there is no way of directly measuring flow through an interatrial septal defect instant by instant during a cardiac cycle, but it may be presumed that the magnitude of the shunt does vary cyclically. In the absence of direct measurement, logical conclusions concerning such cyclic flow changes may be drawn from the available data, including the cyclic pressure gradient across the interatrial septum, but cannot, of course, be regarded as proved. It is possible, for example, that intangible factors such as changes in the size of the interatrial defect during the cardiac cycle may alter the relationship between flow and the pressure gradient across the septum to a significant degree. Here, such a relationship must be regarded as constant. One concept of cyclic flow across the interatrial septum in cases of uncomplicated interatrial septal defect may be expressed as follows:

Blood enters the atria from the cavae or pulmonary veins continuously during the cardiac cycle except during atrial systole, and venous return is much greater to the left atrium than to the right in the presence of an uncomplicated interatrial septal defect. Venous return is augmented for a time after atrial systole, both to the left[1, 15, 30] and to the right atrium.[12] This is attributed to relaxation of the atria, and, in the case of the reduced right atrial inflow, to the intrathoracic pressure changes resulting from expulsion of blood from the thorax by left ventricular ejection. At this time the left-to-right pressure gradient across the interatrial septum is large, and this gradient is maintained, despite the defect, by the constantly replenished reservoir of blood present in the left atrium and its tributaries. The large sustained left atrial inflow and the high left-to-right interatrial pressure gradient therefore suggest that the left-to-right shunt is large, particularly since the A-V valves are closed during this part of the cardiac cycle. The fact that in the experimental animal the creation of a septal defect of moderate size leaves the pressure gradient between the atria virtually unaffected supports this idea, ruling against resistance to flow through the defect as being an important cause of the pressure gradient; this fact further suggests that the left atrium and its tributaries do not at this time contain more than their usual blood volume, the excess having passed through the defect. The greater distensibility of the right atrium allows this excess to collect with little or no rise in right atrial pressure.

About the time that the A-V valves open, the left-to-right pressure gradient decreases rather abruptly and may disappear. It follows that the opening of the A-V valves nullifies or minimizes the factors which were responsible

for the pressure gradient. This is the period of rapid filling of the ventricles[31] when almost all the blood which will make up the systemic flow is entering the left ventricle from the left atrium. The left atrium now has an additional outlet through which a large flow is occurring and venous return is unchanged or reduced. This combination of factors along with the fall in the interatrial pressure gradient indicates that flow through the interatrial septal defect is reduced during the period of rapid inflow of the ventricles. The systolic murmur of uncomplicated interatrial septal defect may be due to the occurrence of most of the shunt during the relatively brief period of ventricular systole.

The foregoing interpretation is in keeping with the radiologic and autopsy observations that the right atrium in cases of uncomplicated interatrial septal defect may be markedly dilated while the left atrium is little altered from the normal. The greater the proportion of the total flow across the interatrial septum in systole, the more dilated the right atrium should be since the excess blood has no runoff while the A-V valves are closed. Thus, the two atria are affected differently by an interatrial septal defect despite the fact that minute flow through each is the same. The basis for such a difference is better appreciated by some consideration of cyclic variations in flow through and between the atria.

The earlier occurrence of right atrial systole as compared with left causes a transient reversal of the pressure gradient across the interatrial septum (figs. 2, 3 and 5). It is likely that much of the small but well-documented[15, 24, 32] right-to-left shunt occurs at this time. During the remainder of atrial systole there is a marked left-to-right pressure gradient. Reversal of the pressure gradient after atrial systole is seen in figures 2 and 3 and is also described by others.[20] Some of the right-to-left shunting may occur at this time.

Apart from the hemodynamics of interatrial septal defect during a typical cardiac cycle, normal and forced respiration play a large role dynamically in artificial interatrial septal defects of animals.[1-5] Although undoubtedly important, this has not been worked out in man.

The right atrial pressure pulse curve shown in figure 1 and used for figure 6 is seen especially in cases of valvular pulmonic stenosis with intact ventricular septum. The precise cause of the augmented "a" wave has not been fully explained.[33]

Consideration of figure 6 with the accompanying blood oxygen data indicates that the cyanosis seen in such cases often has its basis in an intermittent rise in right above left atrial pressure during atrial systole and is not simply due to a general rise in right atrial pressure. Furthermore, venous blood enters the left atrium from the right through a patent foramen ovale with a competent valve rather than through an interatrial septal defect.[34] The valve prevents left-to-right flow of blood while left atrial pressure exceeds the right.

As surgical technics for closure of interatrial defects are more widely applied, it will become important to distinguish preoperatively between interatrial septal defect and a patent foramen ovale in these cases, particularly when cyanosis is present. Such a distinction may be made when the catheter enters the left atrium and a left-to-right pressure gradient is found, in the absence of evidence of left-to-right shunting of blood; or, failing to enter the left atrium, by finding (1) cyanosis or arterial desaturation, (2) a large "a" wave in the right atrial pressure pulse associated with low pressure level during the rest of the cycle and (3) no left-to-right shunt.

Since a probe-patent foramen ovale is usually closed and dynamically insignificant, the routine catheterization of a heart without defects other than patent foramen ovale, or with other dynamically insignificant defects, could by chance reveal the normal human left atrial pressure curve, something which has been recorded only in open-chested man,[35, 36] with the distortion attendant upon recording under these conditions. Such curves obtained in open-chested man without heart disease are roughly similar in contour to left atrial pressure curves from patients with uncomplicated interatrial septal defects and to the left atrial curves recorded in dogs.

From figure 7 it is impossible to be certain whether the short period of left-to-right pressure gradient gave rise to an undetectable

left-to-right shunt through an interatrial septal defect, or whether shunting was prevented by the valve of a patent foramen ovale. The difficulty of determining whether or not a competent valve is present under these circumstances is also illustrated in reported cases in which the right atrial pressure apparently exceeded the left throughout the cardiac cycle.[20]

Certain differences exist between the interatrial pressure gradients of congenital pulmonic stenosis with interatrial communication and those of acute artificial pulmonic stenosis produced in animals along with an interatrial septal defect.[6] Right atrial pressure in the animal is greatest just before the opening of the A-V valves while in the patient it is greatest during atrial systole. Thus, reversal of the left-to-right gradient takes place during one part of the cardiac cycle in a clinical case and at a different time in the experimental analogue. This may be accounted for by dilatation and hypertrophy of the right atrium in congenital pulmonic stenosis which is absent in the acute experimental animal.

The case shown in figure 8 is a clear example of a patent foramen ovale with a competent valve since, with a marked left-to-right atrial pressure gradient, no evidence of a left-to-right shunt was found. A large left-to-right shunt through the interventricular septal defect brings about greatly increased venous return to the left atrium and a decresed return to the right atrium. The left atrium is deprived of the extra outlet present in interatrial septal defect. Since the pressures in the two atria in this case are completely independent, the graph of figure 8 may represent the normal cyclic pressure difference between the two atria in man. More likely, as shown in animal work,[37] the normal pressure difference is exaggerated by the previously mentioned factors, in contrast to its being reduced by an interatrial septal defect.

This analysis shows how the plotting of the cyclic pressure difference between the left and right atrium during the heart cycle may afford a valuable means of studying the cardiodynamics of interatrial septal defect in man as it does in the experimental animal. It permits the evaluation of chronic factors not operative in acute animal experiments. It offers a method whereby a patent foramen ovale in association with other lesions may be recognized on routine catheterization.

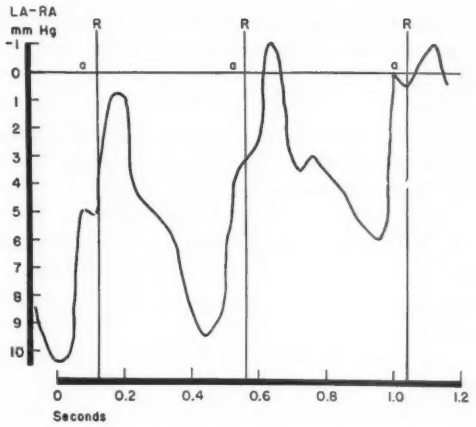

FIG. 8. Cyclic pressure gradient across the interatrial septum in a case of interventricular septal defect and a patent foramen ovale with moderate pulmonary hypertension. Conventions as in figure 2.

SUMMARY

1. The cyclic pressure gradient across the atrial septum was determined in seven cases of congenital heart disease.

2. In general, there is good agreement between data on man and those obtained during animal experiments. The difference found depends on the chronicity of the lesions.

3. Apart from mean pressure differences between the atria in interatrial septal defect, it was shown that pressure fluctuations occurring during one cycle could result in transient reversals of the gradient and so explain the slight arterial desaturation found in these cases.

4. The importance of the cyclic fluctuations in flow, as contrasted with mean flow, has been discussed in connection with the hemodynamics of interatrial septal defect. The striking influence of other congenital lesions on flow through interatrial communications was demonstrated.

5. It is established on dynamic grounds as a result of these studies that the distinction may be made between a patent foramen ovale and

an interatrial septal defect in the living patient even without catheterization of the left atrium.

Sumario Español

1. La pendiente cíclica de presión a través del septo atrial fué determinada en siete casos de enfermedad congénita cardíaca.

2. En general, hay bastante acuerdo entre los datos en el hombre y aquellos obtenidos durante experimentos en animales. La diferencia encontrada depende en la cronicidad de las lesiones.

3. Aparte de diferencias en presión entre los atrios en defectos del septo atrial, se demostró que las fluctuaciones en presión que ocurrieron durante un ciclo podían resultar en reveses transitorios de la pendiente y así explicar la ligera desaturación arterial encontrada en estos casos.

4. La importancia de la fluctuación cíclica en el fluir, al compararse con el fluir promedio, se ha discutido en conección con la hemodinámica de defectos del septo interatrial. La influencia marcada de otras lesiones congénitas en el fluir a través de comunicaciones interatriales fué demostrada.

5. Se ha establecido en bases dinámicas como resultado de estos estudios que la distinción puede hacerse entre un foramen ovale patente y un defecto del septo atrial en el paciente vivo sin necesidad del cateterismo del atrio izquierdo.

Acknowledgments

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Sodium Output–Blood Pressure Relationships and Their Modification by Treatment

By D. M. Green, M.D., and Eugene J. Ellis, M.D.

This study summarizes relationships among blood pressure, 24-hour sodium output, basal output and output under load, in patients on self-selected diets. Additional evidence was secured for the existence of a general correlation between blood pressure and sodium output. This correlation persisted when the blood pressure of hypertensive patients was chronically reduced by medical or surgical therapy.

THE amount of sodium excreted in the urine after a hypertonic saline infusion was previously reported by one of us[1] to be correlated with the mean blood pressure. As a consequence, the hypertensive patients tended to excrete more sodium than did the normotensive controls. This latter finding was confirmed by Birchall and colleagues.[2] We subsequently showed that the tendency of hypertensive patients toward increased sodium excretion could be elicited not only by hypertonic saline loads, but by mannitol and isotonic saline loads as well.[3]

A lower, but still significant, correlation between the blood pressure of patients and their urinary sodium output was also demonstrated under basal conditions.[1] In comparable animal studies we had found that the basal output of sodium was directly proportional to its antecedent intake in the diet.[4] By inference, the relatively high basal sodium output shown by our patients with hypertension was interpreted as indicating an elevated dietary sodium intake. Since the patient group in these studies had been on self-selected diets, an augmented salt appetite was further postulated.

In the present report, these earlier interpretations have been evaluated by studying the 24-hour sodium excretion. The 24-hour output has been related to the mean blood pressure, as well as to the sodium output under basal conditions and under load.

Investigations of sodium output under load have been extended to the effects of antihypertensive therapy on loading responses; outputs under induced pressure reduction have been compared with the responses observed in subjects who spontaneously exhibited comparable blood pressure levels. The details of these studies are described in the sections which follow.

Methods and Materials

The experimental group consisted of 75 subjects, 25 of whom were normotensive at the time of study and 50, hypertensive. The composition of the subject group is shown in table 1. Three of the patients with essential hypertension had been sympathectomized without success three, four and five years earlier, respectively. All subjects had been on self-selected fluid and dietary intakes for one or more weeks prior to study. The number of subjects used in each test procedure varied with the particular procedure, as indicated in the section on results.

Twenty-four-hour urines were collected as follows: The first morning specimen of the collection day was discarded. Urine was then collected throughout the remainder of that day and night. The collection was then completed with the inclusion of the first specimen of the following morning. The total volume was measured. The water output was considered synonymous with the urine output. An aliquot was analyzed for sodium concentration with a flame photometer and the 24-hour sodium output calculated. The height, weight and sitting blood pressures were measured on the morning on which the collection was completed, and the surface area was calculated. Sodium and water outputs were expressed as milliequivalents per square meter of body surface area per minute and as milliliters per square meter per minute, respectively.

From the University of Southern California School of Medicine, Los Angeles, Calif.

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TABLE 1.—*Composition of the Subject Group*

Diagnosis	Code No.	Number of Subjects
No circulatory disease	1	17
Nephritis without hypertension	2	2
Arteriosclerosis without hypertension	3	6
Total normotensive group		25
Essential hypertension	4	36
Malignant hypertension	5	4
Nephritis with hypertension	6	1
Arteriosclerosis with hypertension	7	9
Total hypertensive group		50
Total		75

Basal urine specimens were collected as follows: Food and fluids were withheld from the previous midnight. The time of the first morning urination was noted. After one hour or longer, the subject urinated again and the time was noted. The volume and sodium concentration of this second voiding were measured. The time interval between the first and second urinations was used to calculate the basal rates of sodium and water output.

The technics of the mannitol and 5 per cent salt loading tests have been described in detail.[1, 3] In brief, mannitol was given intravenously in a priming dose of 8 Gm. per square meter followed by a sustaining dose of 75 mg. per square meter per minute. Urine was collected for two or more 20-minute periods following an equilibration interval. Five per cent saline was given intravenously in a dose of 100 ml. per square meter in 25 minutes. Urine was collected for two one-hour periods measured from the beginning of the saline infusion. The rates of sodium and water output under either type of load were also expressed as milliequivalents per square meter per minute and as milliliters per square meter per minute, respectively. The blood pressure was taken every 20 minutes during the collection periods, and averaged. When loading tests were performed on patients undergoing antihypertensive drug therapy, the patient maintained the medication schedule by taking the drugs with a minimum amount of water approximately one and one half hours prior to the start of the test.

Blood pressures were estimated with a mercury sphygmomanometer. The mean pressure was taken as half the sum of the systolic and diastolic pressures.[1]

RESULTS

The 24-hour rate of urinary sodium output (64 observations in 28 patients) was found to be significantly correlated with the basal rate of sodium output ($r_{xy} = 0.430$; $t = 3.63$; $p < 0.01$). A similar correlation was found between the 24 hour and basal water outputs ($r_{xy} = 0.496$; $t = 4.50$; $p < 0.01$). The 24-hour sodium output averaged 0.063 mEq. per square meter per minute, as compared with a basal rate of 0.057 mEq. per square meter per minute. For water, the 24-hour rate was 0.61 ml. per square meter per minute, as compared with a basal rate of 0.63 ml. per square meter per minute. The differences between the 24-hour and basal rates were not significant either for sodium or for water.

The 24-hour rate of sodium output (24 patients prior to antihypertensive treatment) was also found to be well correlated with the rate during the two hours following a 5 per cent saline load ($r_{xy} = 0.616$; $t = 3.67$; $p < 0.01$) (fig. 1).

The average pretreatment 24-hour urinary sodium excretion of 34 hypertensive patients (average blood pressure 197/120) was compared with that of the 25 normotensive controls (average blood pressure 128/81) (fig. 2). The output of the hypertensive group was approximately 35 per cent higher (0.0674 mEq. per square meter per minute, as compared with 0.0498 mEq.). This difference was significant ($p < 0.01$).

The rate of urinary sodium output under

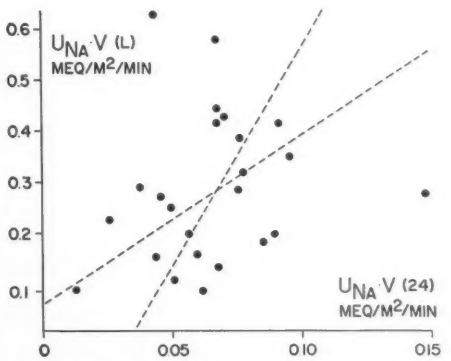

FIG. 1. Relation of the pretreatment two-hour urinary sodium output under 5 per cent saline load to the 24-hour sodium output immediately preceding the loading test ($r_{xy} = 0.616$; $t = 3.67$; $p < 0.01$). The diets of the 24 normotensive and hypertensive patients were self-selected.

TABLE 2.—*Relation of Blood Pressure to Urinary Output under Salt Load in 44 Human Subjects. The Salt Load Consisted of 5 Per Cent Sodium Chloride Solution, 100 ml. Per Square Meter, Given Intravenously in 25 Minutes. The Post-treatment Loading Responses of the Hypertensive Subjects Were Measured in 26 Instances*

Subject		Diagnostic Code Number*	Sex		Age	Blood Pressure			2 Hour Urinary Output Under Load		Treatment†
						mm. Hg			V	$U_{Na} \cdot V$	
			M	F		S	D	M	ml./M.²/min.	mEq./M.²/min.	
MC	(1)	4		x	57	224	110	167	3.65	0.628	None
	(2)					182	102	142	0.24	0.031	HXM 3 Gm./day APR 600 mg./day
JA		4	x		37	184	125	154	3.02	0.579	None
AA		4		x	58	248	141	195	3.52	0.479	None
FM	(1)	4	x		38	241	145	193	2.20	0.479	None
	(2)					197	127	162	1.02	0.203	APR 800 mg./day
	(3)					151	97	124	0.44	0.132	HXM 3 Gm./day APR 800 mg./day
AF		4	x		52	222	137	179	2.03	0.444	None
HG		4		x	40	209	129	169	2.60	0.428	Sympathectomy 3 years previously
FH	(1)	4		x	53	186	105	146	2.21	0.417	None
	(2)					191	95	143	1.37	0.234	APR 600 mg./day
	(3)					173	90	132	1.24	0.183	APR 500 mg./day
RG		4		x	46	192	126	159	2.17	0.416	Sympathectomy 5 years previously
LP	(1)	4	x		51	207	135	171	1.51	0.402	None
	(2)					189	127	158	1.33	0.323	APR 400 mg./day
	(3)					131	97	114	0.47	0.078	Total adrenalectomy; cortisone 25 mg./day
IW		4		x	51	217	113	165	1.73	0.387	Sympathectomy 4 years previously
DM		1		x	32	116	69	93	1.68	0.351	None
LS	(1)	4		x	68	181	86	134	1.96	0.350	None
	(2)					158	76	117	1.71	0.328	APR 400 mg./day
DW		4		x	46	197	111	154	1.67	0.320	None
AJ		2	x		47	140	92	116	1.22	0.291	None
SW	(1)	4		x	26	167	110	139	1.45	0.287	None
	(2)					173	112	143	2.98	0.402	HXM 2 Gm./day APR 600 mg./day
	(3)					126	77	102	0.87	0.156	Subtotal adrenalectomy and sympathectomy
MP		4		x	61	211	115	163	1.06	0.286	None
OR		4	x		52	221	136	179	1.50	0.278	None
JK		4	x		69	219	118	169	1.70	0.272	None
EH		4		x	65	205	117	161	1.06	0.256	None
FN	(1)	4		x	47	213	130	172	1.09	0.253	None
	(2)					163	103	133	0.51	0.108	APR 800 mg./day
AY	(1)	4		x	72	241	101	171	1.24	0.251	None
	(2)					236	106	171	3.21	0.462	APR 500 mg./day
SD	(1)	4	x		43	203	136	170	1.15	0.231	None
	(2)					198	113	155	0.67	0.112	APR 800 mg./day PVR 1 mg./day
	(3)					212	123	167	1.03	0.179	Same (2nd course)
JA		1		x	33	119	81	100	0.95	0.227	None
AL	(1)	4		x	43	224	156	190	0.83	0.214	None
	(2)					224	156	190	0.54	0.118	APR 800 mg./day
MM		6		x	65	178	104	141	1.36	0.200	None
WC	(1)	4	x		43	200	129	164	0.78	0.199	None
	(2)					157	103	130	0.70	0.163	APR 800 mg./day
TA		4	x		38	238	161	200	1.11	0.195	None

TABLE 2.—*Continued*

Subject	Diagnostic Code Number*	Sex		Age	Blood Pressure mm. Hg			2 Hour Urinary Output Under Load		Treatment†
		M	F		S	D	M	V ml./M.²/min.	$U_{Na}V$ mEq./M.²/min.	
TJ	4		x	40	220	134	177	0.85	0.186	None
EG	1		x	29	118	64	91	1.02	0.184	None
ES	1		x	48	130	84	107	0.66	0.184	None
EG (1)	4		x	43	147	115	131	0.87	0.171	Subtotal adrenalectomy and sympathectomy
(2)					151	107	129	0.74	0.152	As above
AS	1		x	46	127	84	106	0.67	0.160	None
JF (1)	4		x	42	162	92	127	0.98	0.150	None
(2)					151	87	119	0.72	0.134	APR 600 mg./day
JH	4	x		39	163	104	134	0.73	0.136	None
LP (1)	4		x	65	161	104	132	0.48	0.129	None
(2)					141	88	114	0.59	0.131	APR 400 mg./day
(3)					160	102	131	0.57	0.157	APR 600 mg./day
AO'H	4		x	40	174	111	142	0.99	0.127	Subtotal adrenalectomy and sympathectomy; cortisone 50 mg./day
EA	4	x		53	152	117	135	0.80	0.124	None
RD (1)	4	x		48	216	129	173	0.54	0.117	None
(2)					126	84	105	0.37	0.072	Total adrenalectomy; cortisone 12.5 mg./day
JJ (1)	5	x		46	167	120	144	1.18	0.111	None
(2)					135	101	118	0.65	0.032	Subtotal adrenalectomy and sympathectomy; cortisone 20 mg./day
WD	2	x		40	106	66	86	0.53	0.093	None
IC	5		x	39	217	133	177	0.71	0.091	None
AG	4		x	68	203	89	146	0.73	0.090	APR 600 mg./day
JG	1	x		43	135	87	111	0.46	0.088	None
CMc (1)	4		x	63	191	83	137	0.30	0.017	None
(2)					182	81	132	0.46	0.043	APR 800 mg./day

* See table 1 for diagnostic code

† APR = Apresoline; HXM = Hexamethonium; PVR = Protoveratrine

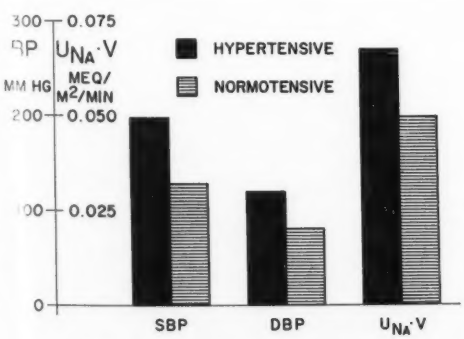

FIG. 2. Blood pressure and 24-hour urinary sodium output of 34 hypertensive patients (average blood pressure 197/120) and 25 normotensive controls (average blood pressure 128/81). The 35 per cent increase in sodium output shown by the hypertensive group was significant ($p < 0.01$). All diets were self-selected.

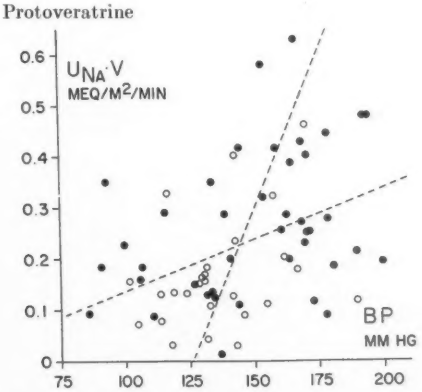

FIG. 3. Relation of the two-hour urinary sodium output under 5 per cent saline load to mean blood pressure ($r_{xy} = 0.403$; $t = 3.55$; $p < 0.01$). The black circles represent pretreatment values in 44 normotensive and hypertensive patients; the open circles, 26 values obtained under various types of anti-hypertensive therapy. All diets were self-selected.

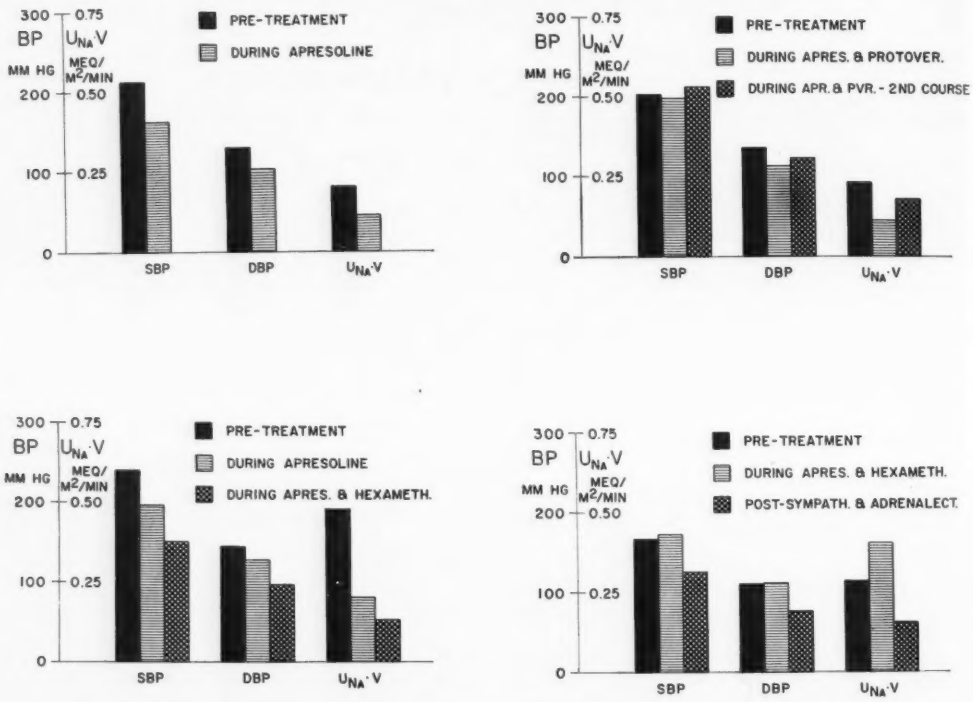

FIG. 4. Relation of blood pressure and urinary sodium output under hypertonic saline load. All values represent the averages of two one-hour collection periods. Sodium chloride, 5 per cent solution, was given intravenously at a rate of 100 ml. per square meter in 25 minutes, starting from the beginning of the first collection period.

SBP = Systolic blood pressure (mm. Hg); DBP = Diastolic blood pressure (mm. Hg); $U_{Na} \cdot V$ = Urinary sodium output (milliequivalents per square meter per minute).

(*Upper left*): Patient F. N., a 48 year old female with long-standing sustained hypertension, who had suffered one cerebral vascular accident. This graph illustrates a moderately low pretreatment sodium output; blood pressure, 213/130. During therapy with Apresoline, 800 mg. per day, the sodium output was reduced to 71 per cent of the pretreatment level; the blood pressure fell to 163/103.

(*Upper right*): Patient S. D., a 43 year old male with hypertension of 10 years' duration. This graph illustrates a moderately low pretreatment sodium output; blood pressure, 203/136. During oral therapy with Apresoline, 800 mg. per day, and protoveratrine, 1.5 mg. per day, the sodium output was reduced to 48 per cent of the pretreatment level; the blood pressure fell to 198/113. Subsequently, treatment was discontinued because of increasing resistance to the hypotensive effect. During a second course of the same therapy, the sodium output increased to 78 per cent of the pretreatment level; the blood pressure rose to 212/123.

(*Lower left*): Patient F. M., a 38 year old male with hypertension of three years' duration. This graph illustrates a relatively high pretreatment sodium output; blood pressure, 241/145. During oral therapy with Apresoline, 800 mg. per day, the sodium output was reduced to 42 per cent of the pretreatment level; the blood pressure fell to 197/127. On addition of oral hexamethonium chloride, 3 Gm. per day, the sodium output underwent an additional reduction, to 28 per cent of the pretreatment level; the blood pressure showed a further fall to 151/97.

(*Lower right*): Patient S. W., a 26 year old female with hypertension of seven years' duration, aggravated by a pre-eclamptic episode four months prior to the first salt load. This graph illustrates a moderately high pretreatment sodium output; blood pressure, 167/110. During treatment with Apresoline, 600 mg. per day, and hexamethonium chloride, 3 Gm. per day, the sodium output increased 40 per cent above the pretreatment level; the blood pressure rose slightly. After lumbodorsal sympathectomy and subtotal adrenalectomy the sodium output was reduced to 54 per cent of the pretreatment level; the blood pressure fell to 126/77.

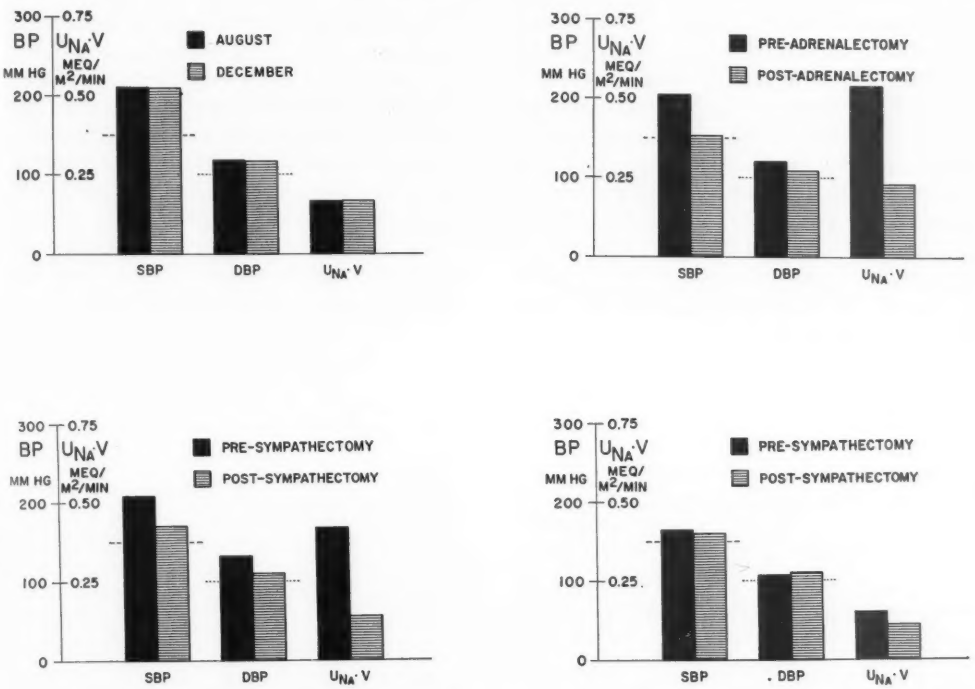

FIG. 5. Relation of blood pressure and sodium output under mannitol load. All values represent averages of two or more 20-minute collection periods. Mannitol was given intravenously at a rate of 75 mg. per square meter per minute, following a priming dose of 8 Gm. per square meter.

SBP = Systolic blood pressure (mm. Hg); DBP = Diastolic blood pressure (mm. Hg); U_{Na}·V = Urinary sodium output (milliequivalents per square meter per minute).

(*Upper left*): Patient U. M., a 50 year old female with long-standing hypertensive cardiovascular disease. This graph illustrates the similarity in sodium output at the beginning and end of a four-month period during which the blood pressure was stable.

(*Upper right*): Patient F. M., a 28 year old female with malignant hypertension. This graph illustrates a relatively high pretreatment sodium output; blood pressure, 205/120. The sodium output after total adrenalectomy was reduced to 40 per cent of the preoperative level; the blood pressure fell to 153/108.

(*Lower left*): Patient E. S., a 36 year old female with sustained, non-malignant hypertension. This graph illustrates a moderately high pretreatment sodium output; blood pressure, 208/132. The sodium output following thoracolumbar sympathectomy was reduced to 30 per cent of the preoperative level; the blood pressure fell to 170/110.

(*Lower right*): Patient D. J., a 38 year old male with malignant hypertension. This graph illustrates a relatively low pretreatment sodium output; blood pressure, 164/107. Lumbodorsal sympathectomy was without significant effect on sodium output or blood pressure.

5 per cent saline load (67 measurements in 44 patients) showed a significant correlation with the blood pressure (r_{xy} = 0.403; t = 3.55; $p < 0.01$) (table 2). In 26 of these instances the sodium excretion rates were measured subsequent to antihypertensive therapy. The urinary sodium output under load after treatment fell into the same pattern of correlation with blood pressure as in the 41 measurements made prior to such treatments (fig. 3). The treatments consisted of Apresoline (14 instances); combination of Apresoline with hexamethonium chloride or protoveratrine (five instances); subtotal adrenalectomy and sympathectomy (five instances) and total adrenalectomy (two instances). When the

blood pressure was significantly lowered as a result of treatment, sodium output under load was also reduced. As a consequence, only about 8 per cent of the loading responses during treatment were above the highest level shown by the normotensive controls, as compared with approximately 33 per cent of the hypertensive group's responses prior to treatment. The tendency of sodium output to follow blood pressure is illustrated in figure 4 for selected individual subjects from the group represented in figure 3.

Comparable results under mannitol loads are shown for individual subjects in figure 5.

Discussion

The results signify that the 24-hour output of sodium tends to be higher in hypertensive patients, as had been previously shown for the output under basal conditions and under various types of load.[1, 3] Since the diets in the present experiments were self-selected, the significantly higher pretreatment 24-hour output of the hypertensive group, who were studied under conditions of stable weight, supports the inference that the sodium appetite of such patients also tends to be increased.

While this description summarizes the behavior of groups of hypertensive patients, the data in these and previous studies emphasize that individual hypertensive patients varied widely from the mean. In some cases the sodium outputs, both basal and under load, were well within the normotensive range, while in others the excretion rates were as much as double the highest normotensive value. Individual differences in the handling of sodium appeared to be magnified by the imposition of loads. Although many speculations might be advanced to account for these variations, the only two factors so far demonstrated to be involved are the absolute magnitude of the blood pressure and the temporal stage of the hypertensive disease. The influence of these factors and their potential significance have been discussed in other papers.[3, 5, 6]

The results in these studies do not demonstrate whether salt appetite is augmented as a compensation for increased renal excretion or whether the converse is correct. However, the profound effect of antihypertensive therapy on loading responses suggests that the excretion of sodium is the primary variable upon which the appetite for sodium is dependent; it seems unlikely that such diverse treatments as Apresoline, hexamethonium, adrenalectomy and sympathectomy would all so alter appetite in the same degree and direction as to uniformly produce comparable secondary changes in the response to salt loads.

Summary and Conclusions

The relation of urinary sodium excretion to blood pressure under various conditions was studied in 75 normotensive and hypertensive subjects. The 24-hour rate of sodium excretion was significantly correlated with both the basal rate and the rate under 5 per cent saline load. The average basal rate did not differ significantly from the average 24-hour rate, suggesting that the basal rate may be used as an index of the over-all intake and output in groups of subjects under conditions which indicate the existence of sodium balance.

The average 24-hour output of the hypertensive subjects prior to treatment was about 35 per cent higher than the normotensive output. Since all subjects had been on self-selected diets and had shown stable weights during this period of observation, the inference was made that the sodium appetite of the hypertensive group was increased as well.

The sodium output under load was found to be well correlated with the mean blood pressure. This relationship persisted when the blood pressure of the hypertensive patient was lowered by medical or surgical treatment. As a consequence, only 8 per cent of the treated hypertensive patients showed loading responses above the highest control value, as compared with 33 per cent of the group prior to treatment. These 8 per cent were comprised of individuals whose blood pressure was not materially reduced as a result of treatment.

Sumario Español

La relación de la excreción urinaria de sodio a la presión arterial bajo varias condiciones fué estudiada en 75 sujetos normotensos e hiper-

tensos. La excreción en 24 horas del sodio correlacionó significativamente con el promedio basal y el promedio de excreción bajo una carga de salina al 5 por ciento. El promedio basal no difirió significativamente del promedio en 24 horas, sugiriendo que el promedio basal puede ser usado como un índice de la ingestión total y excreción total en grupos de sujetos bajo condiciones que indican la existencia de balance sódico.

El promedio de excreción total en 24 horas de los sujetos hipertensos anterior al tratamiento fué como 35 por ciento más alto que la excreción del normotenso. Como todos los sujetos habían estado en dietas seleccionadas personalmente y habían mostrado pesos estables durante el período de observación, la inferencia se hizo que el apetito para el sodio del grupo hipertenso también estaba aumentado.

La excreción del sodio bajo carga se encontró bien correlacionada con el promedio de presión arterial. Esta relación persistió cuando la presión arterial del paciente hipertenso fué rebajada mediante tratamiento médico o quirúrgico. Como consecuencia, solamente 8 por ciento de los pacientes hipertensos tratados mostraron respuestas a las cargas más altas que los valores control más altos, al compararlos con 33 por ciento del grupo antes del tratamiento. Este 8 por ciento fué compuesto de individuos cuya presión arterial no estuvo materialmente reducida como resultado del tratamiento.

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A Theoretic Analysis of the Effects of Dipole Eccentricity upon the Manifest Vectors, the Manifest QRS Loops and the Potential of the Central Terminal

By MANUEL GARDBERG, M.D.

Assuming homogeneous conductivity and a limitless medium, a theoretic analysis accomplished by employing a model leads to the conclusion that dipole eccentricity produces a systematic error in the magnitude and direction of the instantaneous manifest vectors, the manifest QRS loops and the potential of the central terminal. Exaggeration of the electrical rotation of the heart and other electrocardiographic problems are discussed as possible manifestation of dipole eccentricity. Certain correlations applying to spatial vectorcardiography are made from simultaneous study of the theoretic back potential, the AP lead of the cube, and the potential of the central terminal.

IN a previous paper[1] the author reported the results of a theoretic analysis of the errors incident to the assumption that the cardiac dipole remains at the center of the geometric figures commonly employed as frames of reference in vectorcardiographic technic. This study led to the investigation of the Einthoven triangle from the same standpoint. Accordingly, it was felt that it would be advantageous to be able to measure, simultaneously, the three extremity potentials, the potential of the back electrode of the tetrahedron, and the potentials at the two electrodes employed in measuring the anterior-posterior projections of the vectors of the cube.

At the same time that the construction of the model designed for this purpose was completed, Frank's papers[2, 3] on the same subject appeared in the literature. Frank's approach to the analysis of errors introduced into the manifest direction and magnitude of the cardiac potentials by eccentricity of the dipole involved restricting the dipole to the frontal plane and to a single location during the inscription of the QRS complex. Frank indicated, however, that he was completely aware that an anterior-posterior component of the dipole axis would increase the error and also that movement of the dipole during the process of accession would modify the error.

The approach which the author had projected, employing the above mentioned model, involves moving the dipole in three-dimensional space, and studying the effect on the manifest direction and magnitude of the cardiac vector as plotted on the Einthoven triangle. At the same time the potential of the central terminal is studied for each observation. The effects of eccentricity errors as they would appear in the horizontal components of the loops of the tetrahedron and the cube are also investigated.

The employment of a model contributes to greater ease of calculation and to visualization but not to great accuracy of measurement. However, the mathematical formula which might have been employed instead of the model is so cumbersome as to be impractical and it is the writer's opinion that the calculations made from the model are sufficiently satisfactory for the purposes of this study.

METHOD

The method involves the assumption that the wave of excitation may be represented by a single dipole of equal electrical moment located at the center of the wave of excitation. Frank[2] has analyzed one of the errors involved in this assumption. He found that this error is inconsiderable until the angle between the perpendicular to the center of

From the Department of Medicine of the Louisiana State University Medical School and the Department of Medicine of the Touro Infirmary of New Orleans, La.

the wave and the line drawn from the center of the wave to the electrode is less than 18 degrees. Except in discussion this area was not invaded in this analysis. The substitution of the single dipole for the wave of excitation simplifies the formula for calculating the potential at a point, for integration is thus made unnecessary. Further simplification is effected by assuming that the conducting medium is homogeneous and limitless. The formula then becomes

$$V = \frac{E \cos \theta}{d^2}$$

Where E, is the electrical moment of the dipole; θ is the angle between the axis of the dipole and the line drawn from the midpoint of the dipole to the electrode; and d is the distance between the midpoint of the dipole and the electrode.

The model employed is seen in figure 1. The rod, E, is the vector representing the direction of the dipole and the magnitude of the electrical moment of the dipole. Obviously, the magnitude is kept constant in this study. The dipole is located at the center of the rod. This point is connected to the points R, L, F, B, X and Y by elastic cords, which become the lines upon which the vector is projected and upon which the distance from the dipole to each of these electrode positions is measured. R is the right shoulder; L is the left shoulder, F is the left leg, and B is the position of the back electrode of the tetrahedron. X and Y are the anterior and posterior electrode positions employed in the measurement of the anterior-posterior projection of the vectors in the cube method of vectorcardiographic recording. The vector is seen to be double-ended so as to facilitate projection of positive and negative values upon the lines without necessitating the difficult maneuver of extending the lead lines for this purpose. The rod, E, is carried by a carpenter's gage which permits linear movements of the dipole. The carpenter's gage is carried by a vertical quarter-circle made of plywood, which is in turn carried at a 90 degree angle by a similar quarter circle both of which are adjustable. It is thus possible to orient the vector in a multitude of directions and relations to the frontal plane and then study the effects of linear movement of the dipole.

The value of $E \cos \theta$ is obtained by dropping perpendiculars from the appropriate end of the vector (positive or negative) to the line connecting the midpoint of the dipole to the electrode positions R, L, F, B, X and Y, and measuring the projections upon these lines with a metric rule. The distances from the midpoint of the dipole to the electrode positions R, L, F, B, X and Y are measured directly in centimeters. For each observation the values for $E \cos \theta$ (the projection upon the lines) and the distances are tabulated for each of the electrode positions. The theoretic potential at each electrode

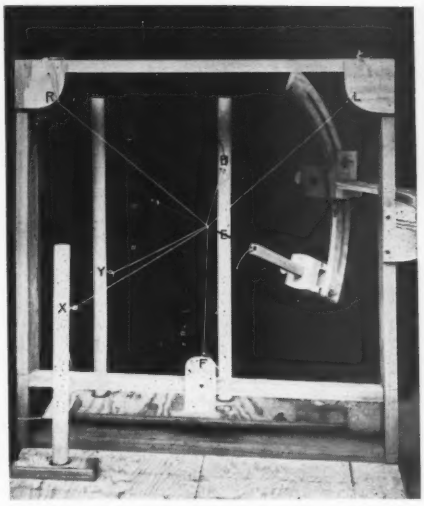


FIG. 1. The steel rod, E, represents the double ended spatial vector of the dipole situated at the midpoint of the rod. The points R, L, and F represent the electrode positions on the right arm, left arm and left leg, respectively, forming the Einthoven triangle. B is the position of the back electrode employed in the tetrahedron technic for spatial vectorcardiography. X is the anterior electrode position and Y the posterior electrode position employed in measuring the anterior-posterior component of the vectors in the cube technic. The dipole is connected to all electrode positions by means of elastic cords. The dipole position pictures in not centric.

was then calculated from the formula $V = E \cos \theta/d^2$. The theoretic potential of the central terminal was then computed for each observation and this subtracted from all potentials commonly measured against the central terminal.

In plotting the manifest vectors on the frontal plane the two largest potentials among V_R, V_L, and V_F were employed. There was no very good reason for not employing the standard limb leads I, II and III except that it would have involved additional tabulation. The results would have been the same.

The method is necessarily subject to error in measurement, but it makes it possible to visualize and to study the general order of the variations due to change of position of the dipole in which we are interested. If the measurements are plotted on coordinate paper against the measured linear movements of the dipole, it becomes possible to recognize as inaccurate those measurements which fail to fall on a smooth curve of the general form shown in figure 2. This set of curves was derived from a previous analysis.[1]

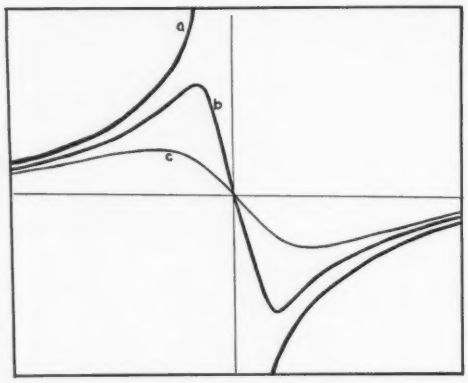


FIG. 2. Curves derived from a previous analysis[1] showing the potential variation as a dipole moving in the line of its own axis approaches and passes an electrode position (a) when the electrode is on or close to the line of motion; (b) when the electrode is moved further away from the line of motion, and (c) when the electrode is at a still greater distance from the line of motion.

One question which arises immediately involves the location of the frontal plane. For most of the purposes in this analysis it is assumed that the frontal plane is located 4.5 cm. behind the anterior wall of the chest and that the remaining 16.5 cm. of the anterior-posterior diameter of the chest lies behind it. Various opinions will be expressed regarding this point. The frontal plane may actually be so far back as to divide the chest into anterior and posterior halves. This problem will be taken up in the discussion.

RESULTS

Results in Radial Eccentricities

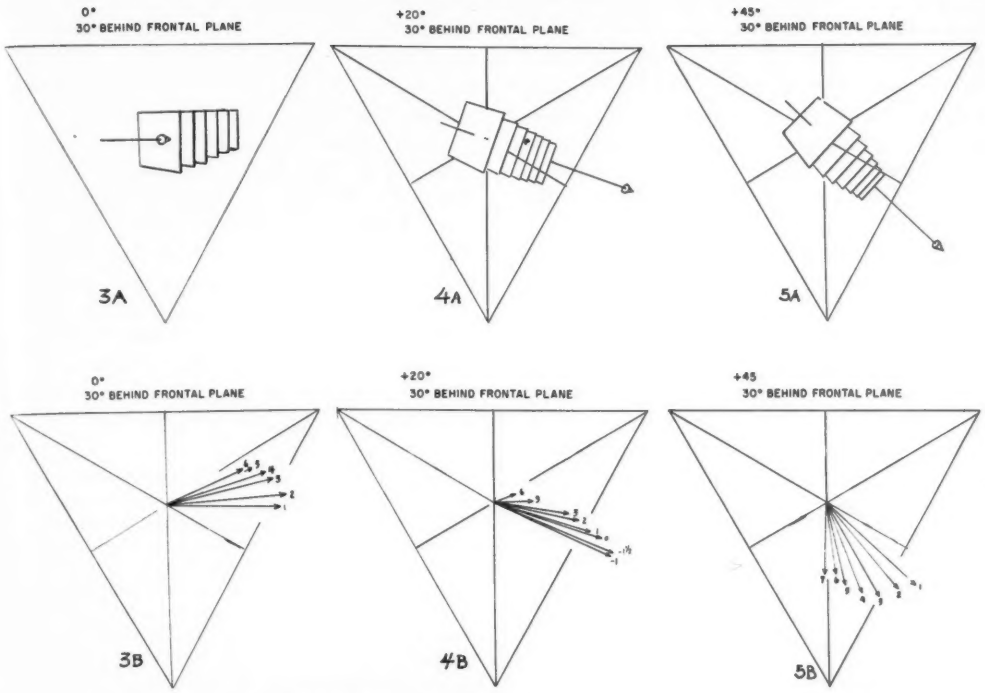
The first motion of the wave of excitation studied is depicted in figures 3*A* and 3*B*. The axis of the vector is at 0 degrees in its frontal plane projection and in space it points 30 degrees behind the frontal plane (antero-posterior component). As shown in the figure the first position is centric. The reader is looking at the negative surface of the wave of excitation. Each succeeding position studied is 1 inch back and to the left of the preceding one. The motion is in the spatial direction of the vector and is accomplished simply by moving the slide of the carpenter's gage 1 inch for each change of position. The parallel positions of the wave of excitation as shown in figure 3*A*, are regarded as possible positions of waves of excitation in the right ventricle septum or left ventricle in various human hearts.

The manifest vectors resulting from the study of this motion are seen in figure 3*B*. The vector numbered 1 is the manifest vector for the centric position of the dipole. The vectors numbered 2, 3, 4, 5 and 6 result from moving dipole to the progressively more eccentric positions as described above. The vector, 1, for the centric dipole possesses the correct magnitude and direction. It is to be noted that as the wave of excitation moves backward and to the left the manifest vector rotates counterclockwise and becomes progressively shorter (see vectors 1 to 6, fig. 3*B*).

In this motion the dipole is not depicted as occupying a position anterior to the frontal plane. This is regarded as a deficiency. In the succeeding studies this deficiency is remedied.

Figures 4*A* and 4*B* show the results of a study of the same kind of motion of a dipole whose representative vector in space is at +20 degrees, as projected on the frontal plane, and again 30 degrees behind the frontal plane. Here, again, the manifest vector is seen to rotate counterclockwise with increasing degree of eccentricity. It also becomes shorter if we consider only those vectors representing the centric position in the frontal plane, vector 0 of figure 4*B*, and the succeeding positions behind the frontal plane, vectors 1, 2, 3, 5 and 6 of the same figure. These do not at first rotate counterclockwise as rapidly as was seen for the first motion studied at 0 degrees, but they become shorter more rapidly. The two positions designated by the negative numbers, $-1\frac{1}{2}$ and -1, are anterior to the frontal plane. Their manifest vectors are rotated clockwise from the true direction represented by the vector 0, and they are longer.

Figures 5*A* and 5*B* show the variation of the magnitude and direction of the manifest vector when the actual vector is again pointing 30 degrees behind the frontal plane and its projection on the frontal plane is +45 degrees. Here we note that the manifest vectors for the eccentric positions rotate clockwise in contrast to those of the previously studied motions. They become shorter less rapidly than those



FIGS. 3*A* and *B*. The spatial axis of the dipole is at 0 degrees as projected on the frontal plane and the angle between the dipole axis and the frontal plane is 30 degrees. The direction of the eccentric movement is the same as the axis of the dipole. The upper diagram furnishes a spatial visualization of the waves of excitation producing the manifest vectors shown in the lower part of the figure. The reader is looking at the negative surfaces of the waves of excitation. As the dipole moves to more and more eccentric positions it is seen that the manifest vectors deviate counterclockwise in direction and become smaller in magnitude.

FIGS. 4*A* and *B*. The spatial axis of the dipole is at +20 degrees and the angle between the dipole axis and the frontal plane is 30 degrees. The eccentric motion has this same direction. It is seen that as the wave of excitation is moved leftward from the centric position to more and more eccentric positions, as visualized in the upper part of the figure, the manifest vectors shown in figure 4*B* deviate more and more counterclockwise in direction and become smaller. The deviation in direction is smaller than for the dipole at 0 degrees and eccentricity in the same axis, but the change in magnitude of the manifest vectors is greater. Movement of the dipole to the right and anterior to the frontal plane, vectors $-1\frac{1}{2}$ and -1, causes the manifest vectors to deviate clockwise and become longer.

FIGS. 5*A* and *B*. The spatial axis of the dipole is at +45 degrees as projected on the frontal plane and the anterior-posterior component of the dipole axis is again 30 degrees. The direction of the eccentricity is the same as the axis of the dipole. It is seen that as the dipole becomes more eccentric to the left of center, the manifest vectors deviate *clockwise* in direction and become smaller.

for the dipole at +20 degrees (fig. 4*B*), and more rapidly than those for the actual dipole at 0 degrees (fig. 3*B*).

Discussion. It is important to note that the motion passes through the center of the Einthoven triangle in the frontal plane. It is also important to note that dipole axes form a 30 degree angle with the frontal plane and point backward and that the motion also has this same direction. Thus, in the motions depicted above, as the dipole moves away from the center of the triangle it not only increases its distance from the center as projected on the frontal plane but at the same time *increases its distance from the frontal plane*. Both distances are important, for both alter the spatial relationship of the dipole to the electrode positions.

It is apparent from the results shown above

that radially eccentric positions of the dipole in three dimensions produces marked deviation in both the magnitude and the direction of the manifest vector. When the axis of the dipole and the direction of the motion is at +45 degrees, the deviation in direction is clockwise. When the direction of the dipole and motions is at +20 degrees, and at 0 degrees, the deviation is counterclockwise. It is evident that at some intermediate axis the deviation of direction of the manifest vector must fail to occur. Geometric consideration alone makes it clear that a simple radial motion of a dipole whose axis, as projected upon the frontal plane, is at +30 degrees will produce no error in direction at all. In figure 6 it is apparent, if the dipole has a radial direction of +30 degrees as projected upon the frontal plane and moves in the same direction in the linear manner employed in this study, R_1 to R_2, etc., that as the dipole becomes more and more eccentric the projection ($E \cos \theta$) of the vector upon the line joining the midpoint of the dipole to L will remain equal to the corresponding projection for F as both diminish rather rapidly. At the same time the distance, as it shortens, also remains equal for both electrode positions. As a result the potential at F will always equal the potential at L, and the direction of the manifest vector remains the same throughout the motion; but the magnitude diminishes rapidly, since the potentials are reduced rapidly at L and F and also at R (the same conclusion applies to dipoles of radial direction at axes, −90 degrees and at +150 degrees). With the dipole pointing in the opposite direction from +30 degrees, −90 degrees, and +150 degrees, i.e., toward the apices of the triangle, and with the same direction for the radially eccentric motion (toward the apices of the triangle), there is also no deviation of direction of the manifest vector, but in these cases the magnitude of the manifest vector behaves in a different manner for *it usually becomes longer with increasing eccentricity.*

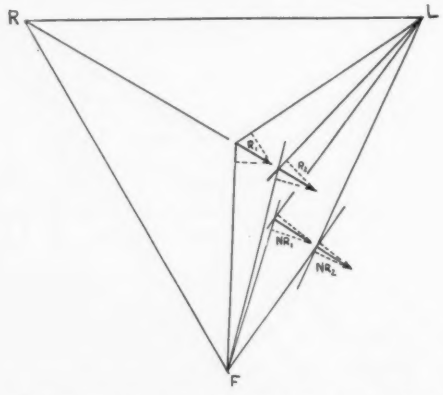


FIG. 6. This figure depicts the effect of a radial dipole, R, and of a nonradial dipole, NR, both at +30 degrees, on the potentials at L and F as the dipole becomes more and more eccentric toward the left. Further description in text.

Here it becomes important to consider separately the effect of the relationship of the dipole to the frontal plane. (See fig. 7.) We shall consider the dipole of axis +90 degrees as projected in the frontal plane and the effect of eccentricity upon the magnitude of the manifest vector when the dipole remains in the frontal plane, when it remains behind the frontal plane, and finally when it is anterior to the frontal plane. If the dipole whose axis is at +90 degrees as projected on the frontal plane (see fig. 7) remains *in* the frontal plane as it approaches F, the magnitude of the potential at F would follow a hyperbolic function for degrees of eccentricity applicable to the human heart (fig. 7) even if the dipole has some backward direction. Under these conditions the magnitude of the manifest vector actually increases. Even though the potentials at L and R are diminishing at the same time, they do not compensate entirely for the effect of increase of the potential at F upon the magnitude of the manifest vector. This is due largely to the fact that increasing eccentricity toward F increases the distance between the dipole and the electrode positions R and L, but not as rapidly as it decreases the distance from the dipole to F. However, if the dipole is *behind* the frontal plane and points considerably backwards, and if it is also at some distance from the frontal plane (fig. 7) or becomes so as it moves to more and more eccentric positions, the curve for the potential at F may change to the curve 60 degrees PFP (fig. 7). Under these conditions the magnitude of the manifest vector will first tend to become greater and then to diminish as the degree of eccentricity increases. In the writer's opinion the largest vectors which occur during the inscription of the QRS complex in the normal heart have a considerable backward direction when the projection of the axis upon the frontal plane is at +90 degrees.

On the other hand, if the dipole is anterior to the frontal plane and has the same axis of +90 degrees

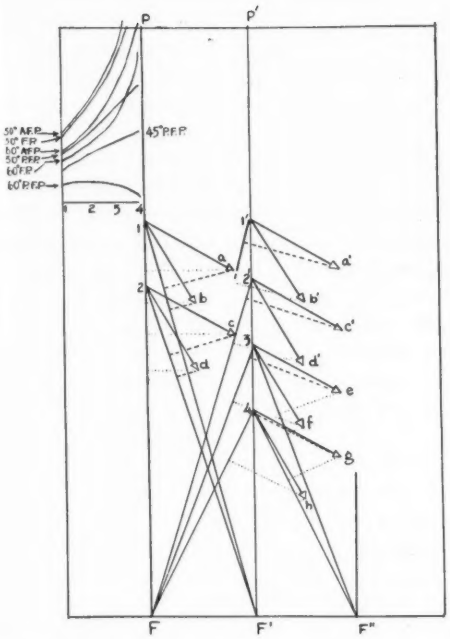


FIG. 7. The rectangular border of the figure represents a sagittal view of the chest. The lines PF and P'F' represent, respectively, an anterior and a mid-position of the frontal plane. F is the location of the left leg electrode for frontal plane, PF and F' is the location of the left leg electrode for frontal plane, P'F'.

The figure represents a series of dipoles 1', 2', 3 and 4, all having an axis of +90 degrees as projected on the frontal plane, and each closer to the left leg electrode than the preceding dipole in the series. The motion of the dipole is studied first when its axis has an anterior-posterior component of 60 degrees represented by vectors a', c', e and g, and then again giving the axis of the dipole an anterior posterior component of 30 degrees represented by vectors b', d', f and h. The effect of the downward movement of the dipole when the dipole is anterior to the frontal plane is studied by measuring the theoretical potentials produced at F' by dipoles 1 and 2, and at F" by dipoles 3 and 4. The effect of the movement of the dipole when the dipole is posterior to the frontal plane is studied by measuring the theoretic potential produced at F by dipoles 1', 2', 3 and 4. The effect of the movement of the dipole when the dipole remains *in* the frontal plane is studied by measuring the theoretic potential produced at F' by dipoles 1', 2', 3 and 4.

The curves in the upper left hand corner show the variation of the potential at the left leg electrode under the conditions indicated by the labels: *30 degrees A.F.P.*, the dipole axis has an anterior-posterior component of 30 degrees, and the dipole is anterior to the frontal plane; *30 degrees F.P.*, the dipole axis has a 30 degree anterior-posterior component and remains *in* the frontal plane; *30 degrees P.F.P.*, the dipole axis has an anterior posterior component of 30 degrees and remains behind the frontal plane. The other labels correspond.

as projected on the frontal plane, and if it has, again, the same backward component as just described for the cases at some distance behind the frontal plane, the magnitude of the potential at F will be greater than is the case for the similarly directed dipole behind the frontal plane, and with increasing eccentricity the potential at F will increase in a hyperbolic order (curve 60 degrees AFP, fig. 7) even though the dipole is at some distance from the frontal plane. Thus, if the dipole is anterior to the frontal plane such eccentricities may be expected to produce a magnification of the magnitude of the manifest vector, but the manifest vector for the dipole anterior to the frontal plane will be smaller than the manifest vector for the dipole in the frontal plane because of the effect of the anterior position of the dipole in reducing the potentials at L and R, when the dipole axis has a backward component. Figure 7 illustrates these points.

If the dipole is rotated away from the +90 degree axis, e.g., toward a +75 degree axis, maintaining its same backward direction, the effect upon the potential at F is the same as increasing the angle between the axis of the dipole and the frontal plane; the spatial relationship of the dipole to F is changed so that the curve for the potential at F at first rises with increasing radial eccentricity and then descends (curve 60 degrees PFP, fig. 7). It must also be noted that as the axis of the dipole is swung away from the +90 degree axis, e.g., to +75 degrees, the influence of the other two electrodes upon the magnitude of the manifest vector begins to increase. The effect of these two factors is that at first the manifest vectors increase, and then they decrease with increasing eccentricity (fig. 11*B*). When the dipole axis is swung to +45 degrees the manifest vectors simply decrease in magnitude with increasing eccentricity (fig. 5*B*).

It is important to note that when the dipole axis is swung away from the +90 degree projection on the frontal plane as just described, changing its position with reference to the frontal plane also alters the direction as well as the magnitude of the manifest vector. Measurements were made which involved keeping constant the spatial axis of the dipole and its eccentric position as projected on the frontal plane, while the dipole was moved in a line perpendicular to the frontal plane from positions anterior to positions posterior to the frontal plane. In all cases the anterior-posterior component of the dipole axis was 30 degrees and the dipole pointed backward. When the axis of the low left eccentric

dipole was at +65 degrees as projected upon the frontal plane, then moving the dipole anterior to the frontal plane produced a shortening of the magnitude of the manifest vector and a reduction of the clockwise deviation in its direction. When the dipole was moved back of the frontal plane the magnitude of the manifest vector diminished again, but more rapidly, and its direction again swung toward the true direction. With the axis of the dipole at 0 degrees as projected on the frontal plane, movement anterior to the frontal plane produced the same effect on both magnitude and direction of the manifest vector. Movement of the dipole of 0 degree axis back of the frontal plane causes the manifest vector to become more counterclockwise in direction and larger in magnitude. With the dipole at the low left eccentric position and the axis at +30 degrees as projected on the frontal plane, moving the dipole forward had only slight effect on either magnitude or direction. However, these effects depend upon the degree of eccentricity and the magnitude of the anterior-posterior component of the dipole axis.

We arrive, then, at the conclusion that if the spatial vector of an eccentric radial dipole behind the frontal plane and at fixed angle with the frontal plane (of say 30 degrees) is swung about the center of the triangle so as to describe a truncated cone whose projected apex is at the center of the triangle, (fig. 8), the following phenomena will be noted:

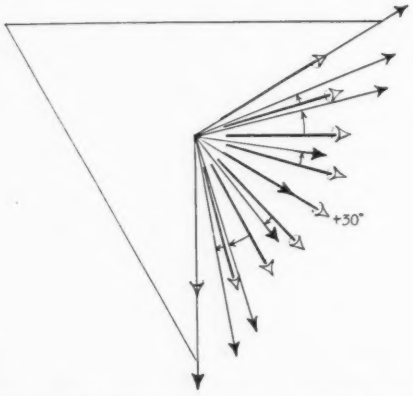


FIG. 8. The figure shows only the general order of the eccentricity effects as the axis of the dipole is changed from +90 degrees to −30 degrees as projected upon the frontal plane. The solid tipped vectors of eccentric point of origin represent the true spatial axis of the dipole. The black tipped vectors are the corresponding manifest vectors. Neither the extent of deviation of direction nor variation in magnitude of the manifest vectors is intended to be quantitative.

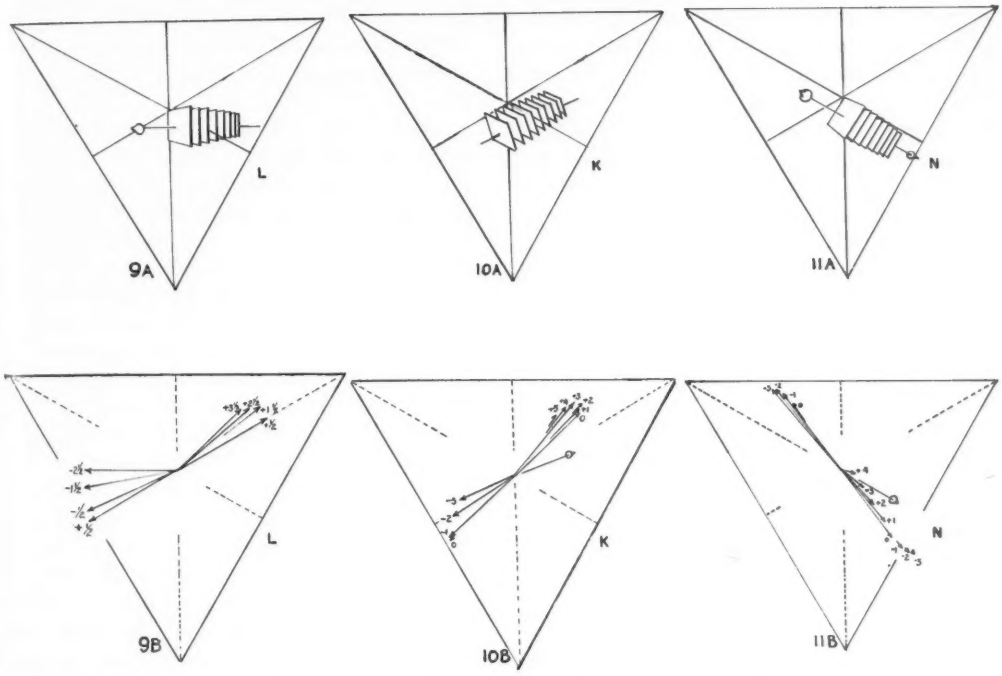
The *direction* of the manifest vector at +90 degrees will not be deviated. As the spatial vector swings to the left (the reader's right) the direction of the manifest vector is deviated clockwise, at first slightly. As the spatial vector is swung further to the left the extent of the deviation in direction increases. As the spatial vector approaches the +30 degree axis the deviation diminishes again and when the +30 degree axis is reached, the deviation is again 0. As the spatial vector is swung to the left of +30 degrees the deviation becomes *counterclockwise* and is first small, then large, and finally small again until the −30 degree axis is reached where again no deviation occurs (fig. 8).

With the spatial vector at +90 degrees the *magnitude* of the manifest vector is greater than would be expected for the centric dipole. As the spatial vector swings toward +30 degrees, as projected on the frontal plane, the magnitude diminishes. At +30 degrees the magnitude is at its minimum, and then it begins to increase again. The same cycle is repeated through each 60 degrees of the 360 degrees.

Increasing the degree of eccentricity, as projected upon the frontal plane, increases the extent of the changes in direction and magnitude of the manifest vector described above.

Increasing the anterior-posterior component of the axis shortens the manifest vector for any position of the dipole. In addition, if the anterior-posterior component is large, it may cause a dipole pointing toward the neighborhood of an apex of the triangle to produce a manifest vector which first lengthens and then shortens with increasing eccentricity instead of becoming progressively larger (fig. 9*B*).

If the dipole positions and directions depicted in figure 8 are moved anterior to the frontal plane the extent of the deviation in direction diminishes and the magnitudes of the manifest vectors diminish. Usually the manifest vectors are larger when the dipole is in the frontal plane than when the dipole is in either the



FIGS. 9*A* and *B*. A low left nonradially eccentric motion of the dipole whose axis is at 0 degrees as projected upon the frontal plane and making an angle of 32 degrees with the frontal plane. As compared with the radial dipole of similar spatial axis (figs. 3*A* and 3*B*), the counterclockwise deviation of the direction is greater. The vectors bearing the negative signs correspond to those of figure 9*B*.

FIGS. 10*A* and *B*. The figures depict the low left nonradial eccentricity when the dipole axis is −20 degrees as projected on the frontal plane and the anterior-posterior component of the dipole axis is 55 degrees. The manifest vectors are seen to be deviated counterclockwise. The magnitude of the manifest vector becomes larger, and then smaller with increasing eccentricity.

In this figure the vectors labeled −3, −2 and −1 represent the manifest vectors for dipole positions anterior to the frontal plane and they are plotted after reversing the signs of the limb potential because these positions are felt to be applicable only to waves of excitation in the right ventricle. The vector in the frontal plane labeled 0 is plotted with and without reversed signs. In the most anterior position (−3) the dipole is anterior to the center of the triangle. The vector is smaller but has the true direction.

FIGS. 11*A* and *B*. The low left nonradial motion of a dipole whose spatial axis is at 30 degrees as projected on the frontal plane and making an angle of 45 degrees with the frontal plane. The direction of the vector is deviated first clockwise and then counterclockwise by increasing eccentricity.

anterior or posterior position. However, the exact relationship depends upon the spatial axis of the dipole and the degree of eccentricity.

Results in Nonradial Eccentricities

It would be extraordinary coincidence if all the eccentricities which apply to the human heart were to fall in the above described radial group. The axis of the dipole must frequently be nonradial and the motion which would represent waves of excitation in the right ventricle, interventricular septum or lateral wall of the left ventricle of various hearts must frequently lie below and to the left of the center of the triangle. Accordingly measurements were made with the dipole at axes of −20 degrees, 0 degrees, and +30 degrees, but with the line of motion below the center of

the triangle, so that the position of the dipole as it passes through the frontal plane is to the left of and below the center of the triangle. The anterior-posterior component of the dipole was varied as will be noted.

Figure 10*B* shows the manifest vectors for a dipole whose axis is at −20 degrees and makes an angle of 55 degrees with the frontal plane (a rather large anterior-posterior component) and which moves through a line which passes through the frontal plane 1¾ inches below and 1¾ inches to the left of the center of the triangle.

Figure 9*B* shows the results of similar motion of a dipole of axis 0 degrees, making an angle of 32 degrees with the frontal plane.

Figure 11*B* shows the result of a similar motion of a dipole of axis +30 degrees, making an angle of 45 degrees with the frontal plane.

Discussion. Obviously, with a spatial axis of −20 degrees, the manifest vectors for the nonradial dipole studies (fig. 10*B*) are all deviated more in the counterclockwise direction than would be expected for the radial dipole of the same axis and eccentricity. This is largely due to the downward displacement of the dipole as compared with the radial studies. This caused the direction of the axis of the dipole to point less toward the apex of the triangle than would a radially directed dipole of the same axis. Under these circumstances the deviation of the direction of the manifest vector is greater.

Thus, unlike the radially directed and radially eccentric dipoles for which the directional relationship to the apexes of the triangle is defined simply by the radial axis upon which the dipole lies and the distance from the center of the triangle, these nonradial dipoles must be oriented by defining (a) the radial axis upon which the dipole lies and the distance from the center of the triangle, and (b) the spatial axis of the dipole itself as projected upon the frontal plane. Both factors, as indicated, have their effect upon the manifest vector. This is found in Frank's formula.[2] This same factor, in addition to the large backward element in the direction of the dipole, caused the manifest vector for this motion to become first larger and then smaller with increasing eccentricity, for the reasons given above. (See fig. 10*B*.)

With a dipole of axis 0 degrees, the low, left nonradial motion produces (fig. 9*B*) manifest vectors which are shorter than those of the centric dipole (compare with vector 0, fig. 3*B*) and which deviate rapidly counterclockwise in direction. All positions behind the frontal plane are deviated markedly in direction. The reasons are the same as those given above for the nonradial axis at −20 degrees. The positions most anterior to the frontal plane is almost equidistant from the three electrode positions R, L and F, and, therefore, the manifest vector assumes the true direction.

The low nonradial dipole at a spatial axis of +30 degrees produces, with increasing eccentricity, manifest vectors which deviate first clockwise and then, with increasing eccentricity, counterclockwise (fig. 11*B*). At the same time the vector becomes rapidly shorter, as is true for the radial dipole at +30 degrees. The reason for the change in deviation is made clear by figure 6. Throughout the motion the dipole is closer to F than it is to L. When both electrodes are facing the positive pole of the dipole, the potential at F is greater than at L. This causes the manifest vectors to point more toward F with increasing eccentricity. As the dipole moves behind the frontal plane, the two electrodes are finally facing the negative pole of the dipole, and F is now more negative than L. This causes the manifest vector to deviate counterclockwise. Certainly a similar inference can be drawn regarding eccentric dipoles with axes parallel to, or nearly parallel to, the other medians of the triangle.

Thus, the nonradial eccentric dipoles produce deviations in direction and magnitude of the manifest vector which are related, as might have been expected, to the same factors which were found to influence those produced by radial eccentricities. On the whole the effects of nonradial eccentricities as depicted here are greater than the effects of radial eccentricity.

General Discussion and Application to the Problems of Electrocardiography

Eccentricity and the Manifest Vectors

It is obvious that as a result of eccentricity it is possible to record manifest axes which range from more than +90 degrees to −30 degrees when the range of rotation of the actual vector (or dipole) has been only from 0 degrees to +45 degrees (figs. 3*B*, 4*B*, 5*B*). Furthermore, if we permit the eccentricity to be nonradial the degree of swing of the axis of the dipole necessary to achieve the same range of manifest axes is even less. It is suggested, then, that eccentricity of the dipole accounts for the exaggeration of the electrical rotation of the manifest QRS axis among human hearts, which most of us accepted as a fact years ago but could not account for. Although this is not the proper place to discuss this matter in detail, it should be pointed out that this exaggeration of the electrical rotations does not materially affect the validity of those analyses in which the electrical rotation of the heart has been employed as a factor.

Offhand, in the analysis of an electrocardiogram, it is not possible to know whether the manifest direction of a QRS axis is the true direction as projected on the frontal plane (for a centric dipole) or whether it is an erroneous direction for an eccentric dipole.

Regarding the magnitude of the manifest vector, it becomes clear that the anterior-posterior component of the axis of the dipole is not the only factor which causes the manifest vector to be small, as was formerly thought. In the eccentric position the manifest vector may become small even though it is not pointing very much backward (e.g., fig. 11*B*, vectors 2, 3, and 4). This is an adequate explanation for the fact that the QRS complex in many instances is small in all three limb leads and yet the back potentials do not indicate that the dipoles were pointing very much backward. However, another factor, the potential of the central terminal, enters into this problem.

It is important to point out here that one cannot conclude from the observations which have been made whether the frontal plane lies in the anterior position described above or in the midposition. For the most part within the range of dipole locations applicable to the human heart, the same order of deviation of the magnitude and direction of the manifest vector occurs in both cases; only the absolute magnitude and the extent of deviation of direction change, and these cannot be easily correlated with any measurable factor.

If we permit the waves of excitation (and their representative dipoles) employed in this study to represent the largest wave of excitation which occurs during the inscription of the QRS complex, and if we consider the fact that, among normal hearts, those which have electrocardiograms with maximum axis in the range +65 to +85 degrees have a greater magnitude for that maximum axis than do those with electrocardiograms showing the maximum axis at 0 degrees to −30 degrees, it becomes evident that this may be explained in one of several ways: (1) those with maximum axis at +65 to +85 degrees are centric so that direction and magnitude are correct, while those at 0 degrees to −30 degrees are most eccentric and, therefore, their direction is largely due to eccentricity and the magnitude small for the same reason; (2) those at 0 degrees to −30 degrees may be centric and have their correct direction and magnitude, while those at +65 to +85 degrees are low eccentricities which tend to increase the magnitude and also to rotate them rightward if they are pointing somewhat in that direction; (3) the difference may result from difference in the anterior-posterior component of the vectors; or (4) there may be a combination of two or more of these. Again the position of the frontal plane does not greatly influence the relative values for the manifest vectors at the various axes as projected on the frontal plane except for axes pointing considerably backward.

However, the position of the frontal plane will greatly affect the calculation of the potential of the central terminal. This will be discussed in more detail later.

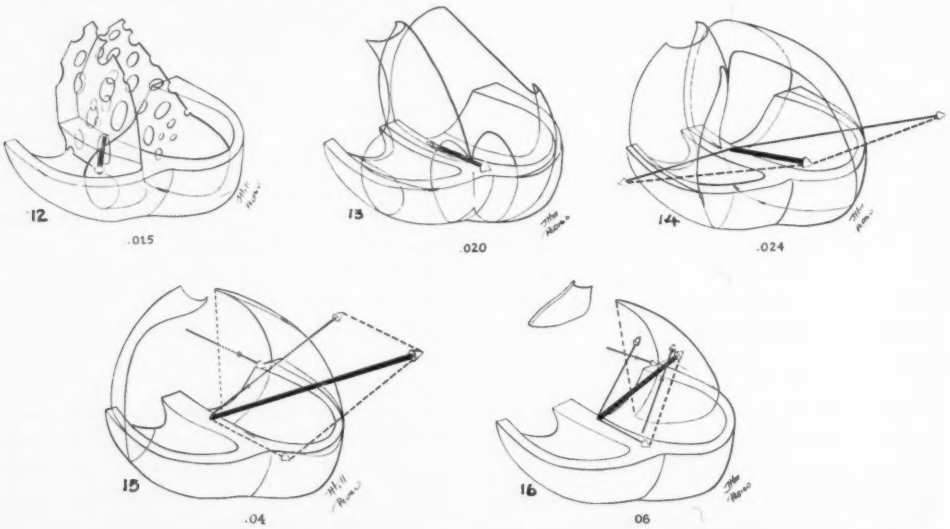
It may be tempting at this point to permit

these manifest vectors of figures 3*B*, 4*B*, 5*B*, 9*B*, 10*B* and 11*B* to represent the mean manifest QRS vectors of various hearts, and it may be proper to do this. However, in dealing with errors resulting from eccentricity, it is necessary to remember that abstractions may not be dealt with in this manner until we are on more solid ground. The mean manifest QRS vector can have little meaning in this connection until we know more about probable effect of the eccentricity errors upon the manifest vector loops.

The Effect of Dipole Eccentricity upon the Manifest QRS Loop

Without pretense at mathematical accuracy we can make an analysis of the probable effect of eccentricity upon the manifest vector loops, if we employ the concept of the path of accession as published by Gardberg and Ashman in 1943.[6] Figures 12, 13, 14, 15 and 16 depict this concept. This publication originated the concept that the actual spatial loop was about twice as long as it was broad and that the long axis of the loop was nearly perpendicular to the anatomic axis of the heart and, therefore, points, in general, to the left and backward in normal hearts. A similar conclusion regarding the general direction of the mean spatial axis of the QRS had been arrived at in an independent analysis of the gradient by Ashman and Byer. The elliptic loop shown, as derived from the waves of excitation of figures 12, 13, 14, 15 and 16, is the result of these analyses and careful trial and error comparison against normal tracings by Ashman. For years we have been employing the method of projecting this model "actual" loop upon a "frontal plane" by means of parallel light (fig. 18) or with the eye in the analysis of electrocardiograms and, in teaching, to show the effects of rotations of the heart on the standard limb leads, as well as in analysis of the ventricular gradient.

Application of the effect of eccentricity on each of the vectors of the five stages of the process of excitation depicted in figures 12, 13, 14, 15 and 16 is shown in figures 17 and 18. Only low left eccentricity effects are employed. The vectors of figure 17*A* represent the



FIGS. 12, 13, 14, 15 and 16. The figures show the wave of excitation at 0.015 second, 0.020 second, 0.024 second, 0.04 second and 0.06 second, respectively. In each drawing the thick vector is the spatial vector derived from the wave or waves of excitation represented. The inaccuracy of such single "dipole" representation for this study is probably not great, but will receive attention in another paper. It is probable that in the right ventricle the wave of accession at 0.024 second has reached the epicardial surface in a larger area than is depicted here.

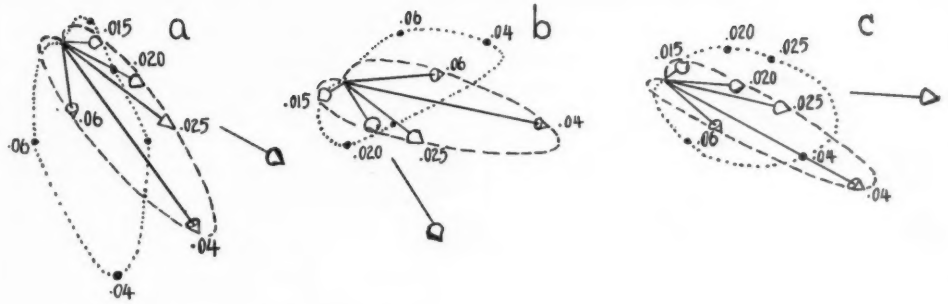


FIG. 17. This figure shows the effect of eccentricity, assuming the center of the heart is below and to the left of the center of the Einthoven triangle. *A* shows the projection of the actual spatial loop (in dashes) of a heart of anatomic axis at +30 degrees and rotated slightly clockwise, the apex of the heart being viewed. The finely dotted loop is the manifest loop which results from the application of the approximated theoretic eccentricity effects. *B* depicts the effects of eccentricity when the anatomic axis of the heart is at +55 degrees and the heart is rotated slightly counterclockwise. *C* depicts the effects of eccentricity when the anatomic axis is at +5 degrees and the heart is rotated slightly clockwise.

successive vectors for the waves of excitation shown above for a heart with anatomic axis at +30 degrees and rotated slightly clockwise about the anatomic axis, H. The loop shown in dashes is, then, the projection of the assumed actual spatial loop on the frontal plane. Assuming that the center of the heart is generally to the left of the midline and below the center of the triangle, the deviations due to eccentricity are approximated by applying to the vectors for each stage of excitation the error which is appropriate to, (1) the spatial direction of the vector, (2) the degree of eccentricity of the wave of excitation represented. Thus, the actual vector at 0.015 second is at about 0 degrees as projected on the frontal plane. The effect of eccentricity upon such vectors is shown on figure 17*A*, the vector being rotated counterclockwise. Since the wave of excitation is in the apexes of the ventricle at this moment, the degree of eccentricity is more than slight. Considerable deviation and some shortening are therefore, assigned to the vector. At 0.02 second the vector is at 25 degrees and the wave of excitation is in the apical half of the heart. Therefore, a deviation in the counterclockwise direction is assigned. The vector at 0.025 second is at +35 degrees and is therefore assigned a clockwise deviation. If it is permissible to represent the wave of excitation by a single dipole, this dipole is not extremely eccentric and the assigned deviation is not great. This will require further analysis. The vector at 0.04 second has an axis of 55 degrees and since the wave of excitation is in the lateral wall of the left ventricle the deviation is clockwise and is of considerable extent. The assigned deviation is to a direction of 78 degrees and the vector is lengthened. A deviation of the vector at 0.06 second is assigned in a similar manner.

The manifest loop is thus represented as the finely dotted loop of figure 17*A*. Thus, it is seen that the effect of eccentricity of the waves of excitation represented in this analysis is to make the loop appear to be wider and directed more toward the +90 degree axis than it actually is. It is important to realize that the effect is the same as would be accomplished by rotating the actual spatial loop more clockwise (fig. 18). Thus the effect of eccentricity is to make the loop appear to belong to a heart rotated more clockwise than it actually is. If the entire heart is moved to a more eccentric position to the left and/or downward from the center of the triangle the effect would be exaggerated.

Figure 17*B* shows the effect of eccentricity in the case of a heart which is rotated slightly

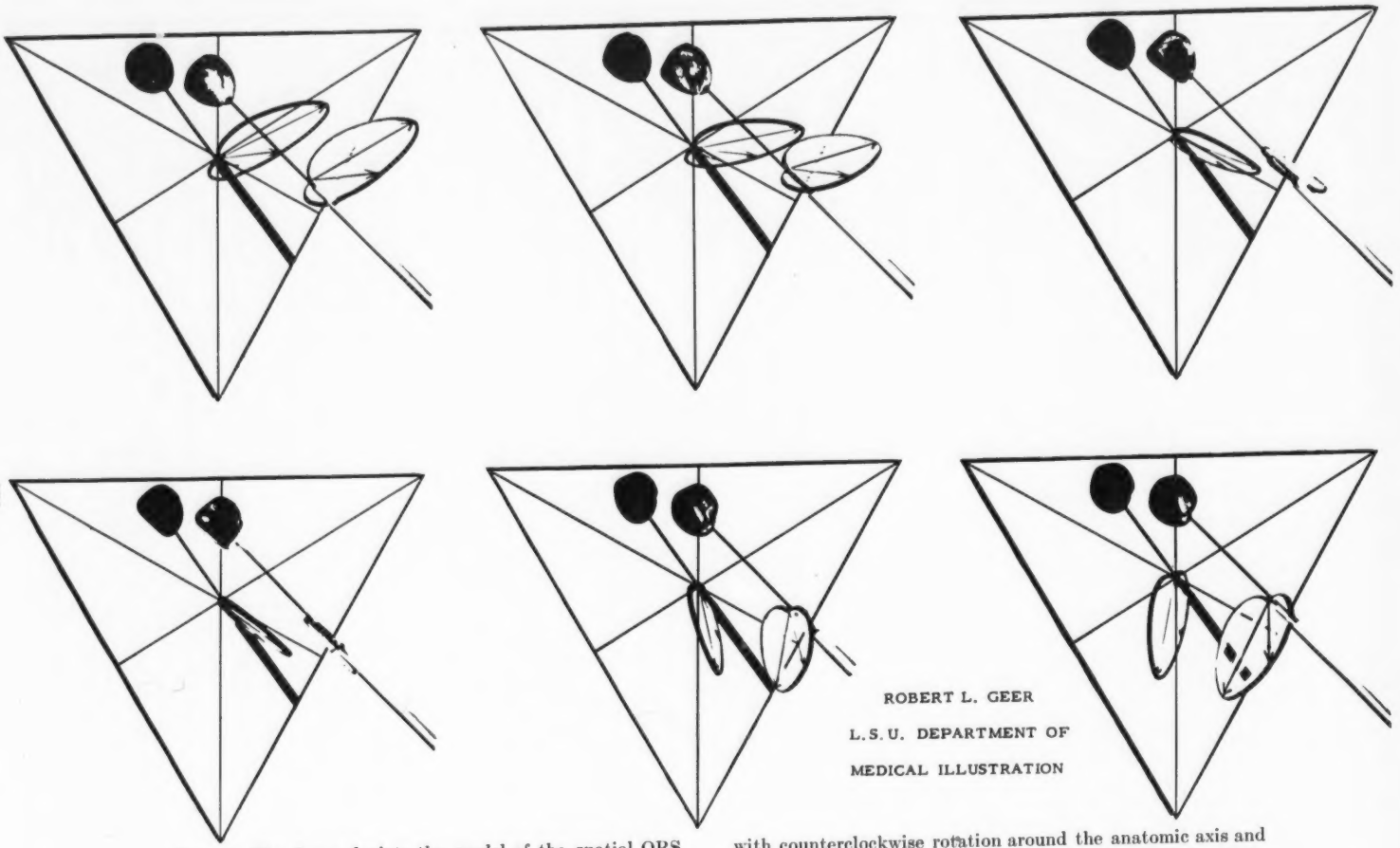


FIG. 18. The figure depicts the model of the spatial QRS loop (made of plexiglas) supported by a plastic rod which represents the anatomic axis of the heart. The wooden model of the ventricles supported by an extension of the rod serves to orient the reader with regard to the degree of anatomic rotation in each photograph. The series of photographs begins (1) with counterclockwise rotation around the anatomic axis and represents six rotational positions ending with strongly clockwise rotation around the anatomic axis. The shadows thrown by parallel rays of light upon the surface of the triangle represent the loops as projected on the frontal plane (the manifest loops as they would appear without eccentricity effects).

counterclockwise, and the anatomic axis is at −55 degrees. It is seen that the effect is to make the loop appear to belong to a heart which is rotated more strongly *counter*clockwise than it actually is.

Figures 19*A*, *B*, and *C* show the vectors of three nonrotated hearts at anatomic axes of +15 degrees, +30 degrees and +45 degrees, respectively. Application of eccentricity effects to these vectors indicates that the more vertical hearts are made to appear to be rotated clockwise while the more transverse hearts appear to be rotated counterclockwise. The loop for the heart at +30 degrees will suffer no deviation in the direction of the manifest vectors if the eccentricities are radial, but the loop will appear to be much shorter (smaller) than it is. The finely dotted loop on the figure for the heart at +30 degrees (fig. 19*B*) is for a nonradial type of eccentricity such as that depicted for the waves of excitation of figure 11*B*. At +15 degrees and +45 degrees nonradial eccentricity will simply exaggerate the apparent rotation.

The above described phenomena indicate that the eccentricity effects upon the manifest loops make it appear that hearts are rotated more than they are and that some are made to appear to be rotated which are not. However, the error seems to follow a definite order and, in the writer's opinion, it is simply the probable mechanism of the exaggeration of the electrical rotations of the heart which for some years some of us have been quite certain existed.

Accordingly, it now becomes possible to regard the vectors of figures 3*B*, 4*B*, 5*B*, 9*B*, 10*B* and 11*B* as mean spatial QRS vectors, for the effect of eccentricity upon the mean direction of the manifest loop seems to be subject to the same definitely orderly error which is summarized in figure 8.

Thus, it appears that the analysis which involves the rotation of a model "actual" loop described above contains this systematic error. It is important to emphasize that the presence of a systematic error in a correlation does not materially affect the validity of the correlation. The same systematic error must be intrinsic in the correlation of the spatial relationship of the anatomic axis, the mean QRS axis and the ventricular gradient, as published by Ashman, Gardberg and Byer. It is suggested that the validity of that correlation is not significantly affected by the presence of the eccentricity error. The potentials which produce the T wave are subject to the same error. This problem will be taken up in another paper.

It is apparent from the above analysis that shortening of the vectors of the loop, and thus of the mean manifest QRS, may result from eccentricity as well as from actual backward direction. Heretofore, foreshortening of the mean manifest QRS has been regarded as an indication of a relatively backward direction of the mean spatial QRS. Since we now know

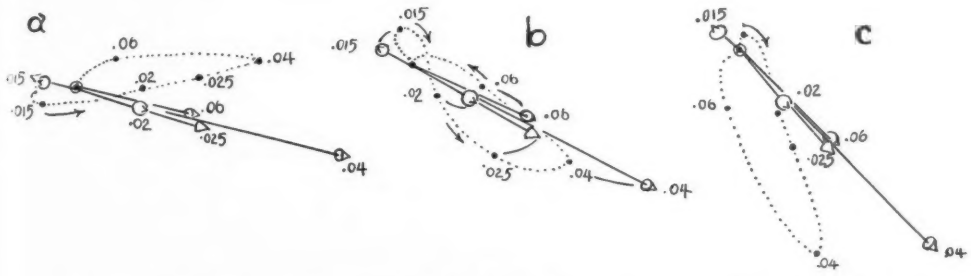


FIG. 19. The solid tipped vectors represent the successive waves of excitation depicted in figures 12, 13, 14, 15 and 16 when the heart is in the intermediate rotational position (not rotated around the longitudinal axis). In *A* and *C* the finely dotted loop is the manifest loop which results from the application of the approximate eccentricity errors, assuming that the eccentricity is of the radial type. In *B* the finely dotted loop results from the application of low nonradial eccentricity effects to the vectors. The manifest vector at .06 second in figure 19*B* should be moved further to the reader's left. This has little effect on the general result.

that this may occur as a result of eccentricity, it is no longer disconcerting to find a discrepancy between the expected and observed back potential. We thus have a probable explanation for the rather low correlation between the back potential and the mean manifest QRS of the frontal plane. The variation of the potential of the central terminal is another factor in this problem.

Two special groups of cases are noteworthy: (1) Figure 17*C*, as stated above, depicts the eccentricity effects when the anatomic axis is at +5 degrees and the heart is rotated a bit clockwise. It is seen here that the effect of the eccentricity is to widen the loop a great deal and to shorten it. This produces the large Q_3 type of electrocardiogram. It has heretofore been somewhat disconcerting that such a projection of our model spatial loop could only be obtained by placing the anatomic axis in a rather improbable position.

(2) Examination of the nonrotated "actual" loop with the anatomic axis at +30 degrees (fig. 19*B*) shows that nonradial eccentricity may cause such a loop to appear to be somewhat folded upon itself. In the same way other loops for hearts with this or similar spatial orientations may be made to appear folded or twisted upon themselves. Such "spatial" loops have been recorded by Burch.

It is not possible to determine the extent to which a recorded manifest loop owes its

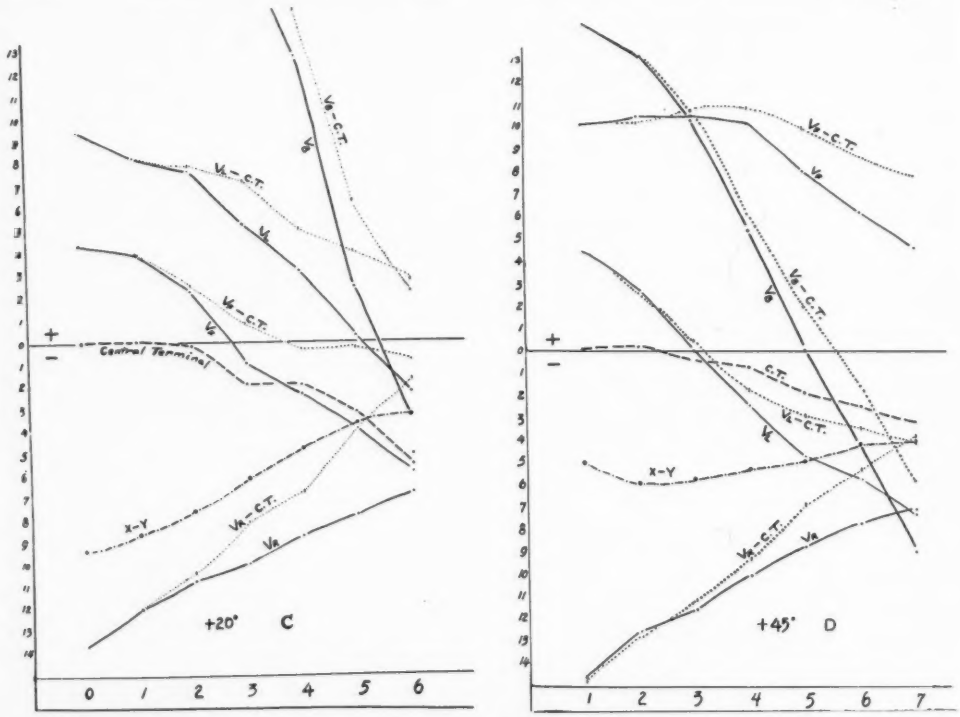


FIG. 20. The curves of each figure result from plotting the tabulations made in each of two studies, as the dipole is moved to more and more eccentric positions represented by the abscissae. V_R. V_L, V_F and V_B are the theoretic absolute potentials at R, L and F and B (see fig. 1). $V_R - CT$, $V_F - CT$, $V_L - CT$ and $V_B - CT$ are the theoretical potentials at V_R, V_F, V_L and V_B measured against the central terminal. X − Y is the difference of potential between the anterior and posterior electrodes employed in measuring the anteroposterior projection of the vectors in the cube technique of vectorcardiography. *C* is for a dipole at axis +20 degrees as projected on the frontal plane. *D* is for a dipole at axis +45 degrees as projected on the frontal plane. In each instance the dipole axis makes an angle of 30 degrees with the frontal plane.

characteristics to eccentricity. It is probable that many loops owe little of their form to eccentricity, while others a great deal. While speculations can be made, actual correlation of individual manifest loop forms with eccentricity as determined from body measurements, including x-rays of the chest is difficult and subject to errors not considered here.

The Effect of Dipole Eccentricity upon the Central Terminal

For each of the dipole positions employed in this study the theoretical potential of the central terminal was calculated according to the formula:

$$V_{CT} = \frac{V_R + V_L + V_F}{3}$$

Figures 20*C* and 20*D* show the effect of increasing radial eccentricity upon the potentials at R, L, F, B, and of the central terminal when the dipole and eccentricity are in the stated axes as projected on the frontal plane. In addition the difference in potential between X and Y, the two electrodes used in measuring the anterior-posterior component of the vectors of the cube, was calculated and these values appear in the same figures. Only the value for dipole in and behind the frontal plane were plotted.

Other results will be described for which no curves were drawn.

Discussion

With the dipole having an axis of +20 degrees as projected upon the frontal plane it is apparent that the potential of the central terminal becomes more and more negative at a rather rapid rate as the dipole is moved to the left and backward. With the dipole at an axis of +45 degrees as projected on the frontal plane, the potential of the central terminal again becomes more and more negative as the dipole is moved to the left and backward in a radial manner, but not as rapidly as it does when the axis of the dipole and of the motion is at +20 degrees. These measurements, together with other measurements which are not reproduced here, indicate that if the axis of the dipole and the motion are swung about as for figure 8 the potential of the central terminal goes through the following changes:

When the axis of the dipole is at +90 degrees and the eccentricity is in the same direction (see fig. 8), the potential of the central terminal is at a maximum. When the axis of the dipole and the eccentricity are in the +30 degree axis, the potential of the central terminal is at its minimum. The order of change is similar to that which characterizes the magnitude of the instantaneous manifest vector. Frank[2] noted this phenomenon.

The absolute value of the potential of the central terminal will depend upon the factors which govern the magnitude of the manifest instantaneous vector. Among these are the anterior-posterior component of the spatial axis of the dipole, and the relationship of the location of the dipole to the frontal plane, that is, whether it is anterior to, in, or posterior to the frontal plane.

The range of values of the potential of the central terminal for the dipole of figure 8, when it is anterior to or in the frontal plane, is from a relatively large positive value at +90 degree axis, as calculated by Frank, to a value in the neighborhood of zero at +30 degrees. The range of values for the central terminal when the dipole is behind the frontal plane is from a slightly positive value at +90 degree axis to a large negative value at +30 degrees. These values may be taken to represent the peak values of the potential of the central terminal during the inscription of the QRS complex for loops having the mean spatial QRS axis represented by the spatial axes of the dipole of figure 8.

Increasing the backward component of the spatial axis of the dipole represented in figure 8 diminishes the potential of the central terminal for all dipole positions and axes represented, if the dipole is in or behind the frontal plane. If the dipole positions as represented in figure 8 are anterior to the frontal plane, increasing the backward component of the dipole axis *increases* the potential of the central terminal. The values for the potential of the central terminal for the dipole positions *in* the frontal plane will be intermediate

between the values for the dipole positions anterior to and those posterior to the frontal plane, especially if the spatial axis of the dipole has a large anterior-posterior component.

It becomes clear that the location of the frontal plane has greater significance for the value of the potential of the central terminal than it has for the absolute value of the manifest instantaneous vector. It is important to realize that the measurement of the instantaneous manifest vectors in practice is a purely relative matter, and therefore their absolute value has no importance. The employment of the potential of the central terminal as a reference in making chest leads for various purposes makes it mandatory that we have some interest in its absolute magnitude. No solution to this problem is offered here.

In Frank's study[2] the axis of the dipole and the dipole were kept in the frontal plane. He also kept the loop fixed, although he gave the eccentricity a large number of directions. Since the dipoles of large electrical moment were kept at axes in the neighborhood of +65 degrees, the calculated potential of the central terminal was found under these circumstances to be generally large and positive. As he pointed out, it is generally much smaller when the dipole positions lie on the +30 degree axis. The circumstances under which he studied the variations are considered by the writer to be unrealistic for the human heart.

Under the circumstances herein considered applicable to the human heart, the order of variation of the central terminal potential during the inscription of the QRS complex must be analyzed on the basis outlined above. Accordingly, the curves of figure 21 show the potential variation of the central terminal which may be commonly reached during the inscription of the QRS complex, when the heart is in an eccentric position which, in the writer's opinion, is appropriate to the indicated mean spatial QRS axis. These are obtained by assigning to the values of the potentials of the central terminal those measurements of the theoretic central terminal potential which are appropriate to the magnitude of the dipole, its location, and its spatial axis during the process of accession as depicted in figures 12 13, 14, 15 and 16.

Since it is at this time impossible to know the location of the frontal plane, no conclusion can be drawn as to whether the set of values depicted in the upper part of the figure or that shown in the lower part actually applies. No ready key to the solution of this problem is offered.

Correlation of Back Potentials with the Mean Manifest QRS Axis

One of the important problems which has been solved in this study, and which was referred to in a previous paper, is the finding by "spatial" vectorcardiographers that many normal QRS loops point forward or parallel to the frontal plane, that the mean back potential is negative or very small, although the actual vectors point backward to some extent, according to our view. This finding had been unexplained until recently, when it yielded to the analysis reported in a previous paper.[1] One correlation remained to be made. This was the one represented by the observation that most loops which were made by the tetrahedron method and pointed forward were vertical in their frontal plane projections, while those which were rounded (and smaller) were more transverse. This phenomenon is revealed, on the curves V_B-CT of figures 20*C* and 20*D*, to be due to the variation of the potential of the central terminal. At +20 degrees, when the dipole is in an eccentric position, V_B is negative but CT is even more negative and, therefore, V_B-CT is positive, making the vector point backward as recorded by the tetrahedron method. At an axis of +45 degrees, and a corresponding degree of eccentricity, V_B is a bit more negative but CT is much less negative than at +20 degrees. Therefore, V_B-CT is negative and the vector points forward as recorded by the tetrahedron method. Actually, of course, the spatial vector points backward as it was made to do throughout this study. No change in amplification can correct for the error in polarity.

Thus, when the spatial axes are in the neighborhood of +30 degrees, the low values (negative here) of the central terminal potential

tend to compensate for eccentricity errors of the back electrode. When the axis and eccentricity are nearer the direction +90 degrees, the absolute value of V_B is more negative and the central terminal is less negative or actually positive, so that V_B-CT is negative and the loop is made to point forward. When the spatial axis is near −30 degrees the absolute value of V_B is so great that the loop points backward in spite of a positive value for the potential of the central terminal.

It is evident from the curves for X-Y of figures 20*C* and 20*D* that the anterior-posterior bipolar lead employed in measuring the corresponding anterior-posterior component of the vectors for the cube do not make nearly as great errors as does the back electrode for the tetrahedron as the latter is commonly employed. No error in polarity is demonstrated on the curves reproduced. Theoretically (and actually) it does occur however, when the anterior-posterior component of the spatial vector is small and/or has a very "vertical axis."

The general character of all these phenomena will be unaltered by changing the position of the frontal plane. As indicated in figure 21, this would change the absolute values of the potential of the central terminal, but would not change the relative values at the different axes and eccentricities.

The variation of the potential of the central terminal, which must take place, but which cannot, as yet, be measured for the purposes of correction, affects all of those methods which employ the central terminal as a reference electrode. The conventional precordial leads employed clinically are probably not erroneous to a significant degree as the result of central terminal error because they are so close to the heart that the potentials are proportionately very much greater than those of the central terminal. However, some phenomena may be explainable on this basis.

On the other hand, any method which employs unipolar leads for the purpose of mathematical correlations, such as determination of the spatial axis of the mean QRS, is fallacious for this as well as for other reasons.

Furthermore, it becomes clear that attempts to derive the precordial potentials from "spatial" loops derived from oscillographic technics are unscientific. It is not within the scope of this paper to discuss all the errors in principle involved in such attempts. However, it must be pointed out that both the precordial leads and the "spatial" loops, considered mathematically, contain significant errors and that these errors are not related to one another. It is true that the errors of the central terminal are related to the Einthoven triangle, but the errors of the back potential employed in the tetrahedron, as well as the potentials of other chest leads, include errors which have no relation to the Einthoven triangle. The cube is in no way related to the central terminal. Again, too many attempts to relate the precordial potentials and potential at other points on the surface of the chest to "spatial" loops have disregarded the factor of time.

It is possible to derive the general form of the precordial leads from the "spatial" loops of the cube as well as from theoretic spatial loops derived from anatomicophysiologic considerations. This may be permissible for teaching purposes, but the errors should be pointed out when the derivation is made.

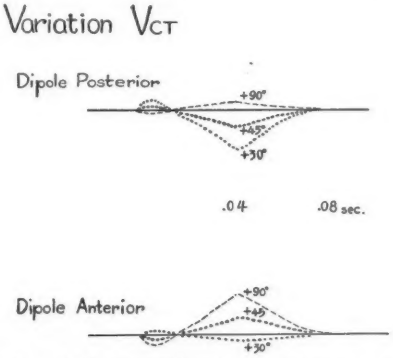


FIG. 21. The curves show the variations of the potential of the central terminal during the inscription of the QRS complex when the mean spatial QRS is at axes +90 degrees, +45 degrees and +30 degrees. The upper set of curves applies when the frontal plane is assumed to be in the anterior position; the lower set applies when it is in the midposition. The maximum potential attained, as shown on the curves, may reach 0.4 the value of the maximum theoretic limb potential found in this study, and is frequently greater than the absolute potential at one or more of the limb electrodes.

Summary

A dipole was moved about in space in a manner which might be applied to electrocardiographic analysis and the effect of this movement (eccentricity) upon the manifest cardiac vector as calculated in the conventional manner was studied. The range of positions of the dipole studied rested on the assumption that the heart is generally to the left or below and to the left of the center of the Einthoven triangle.

Next, the eccentricity effects appropriate to their location in the chest and to their spatial axes were applied to the various stages of the process of accession in the ventricles as represented in the Gardberg-Ashman hypothesis, and the effect of dipole eccentricity upon the manifest QRS loop was approximated.

The theoretic potential of the central terminal was calculated for many dipole positions.

Conclusions

1. In agreement with Frank,[2] it was found that the errors in magnitude and direction of the manifest vector produced by eccentricity of the dipole are considerable. However, these errors follow a definite order and the errors which occur as a result of dipole eccentricity may be described as systematic.

2. As applied to the QRS loop, these errors are found to cause an exaggeration of the electrical rotation of the heart. It is pointed out that the occurrence of this systematic error does not invalidate the correlations made in the past which employed the electrical rotation of the heart as a factor. It is suggested that an understanding of the eccentricity errors may make it possible to understand individual cases in which the correlation was poor.

3. The larger complexes which are seen when the mean QRS axis is +65 to +85 degrees and the smaller complexes when the mean QRS is at 0 to −30 degrees may be in part a result of eccentricity.

4. Small QRS complexes in the limb leads and therefore small, mean manifest QRS vector values, formerly attributed entirely to a larger backward direction of the mean spatial QRS, may be due to eccentricity. It is suggested that this offers an explanation for the finding of small back potentials when the mean manifest QRS axis is small.

5. It is concluded that dipole eccentricity accounts for some of the "twisted" and "folded" loops recorded by spatial vectorcardiographers.

6. A number of individual electrocardiographic problems seem to yield to analysis by application of the effects of dipole eccentricity. A few are described.

7. The potential of the central terminal varies considerably during the inscription of the QRS complex. This may account in part for the curious division of Burch's loops into the two groups which he described. A correlation with the manifest QRS axis is made.

8. On the basis of variation of the potential of the central terminal, the value of any method which employs "unipolar" chest leads for any sort of mathematical correlation or to determine the spatial direction of the mean QRS axis is questioned. Together with other errors involved, this evidence makes it obvious that such methods are fallacious.

Again on this basis the notion that "unipolar" leads reflect the absolute potential at a point and are, therefore, more accurate than bipolar leads is questioned.

It is quite clear to the writer that he has assumed that the conducting medium is homogeneous and that it is limitless. Nonhomogeneity of the conducting medium and the limiting contours of the chest walls will, when their effects become known, modify the results found here. In the writer's opinion these effects will modify the results and conclusions presented here more in a quantitative than in a qualitative manner.

Sumario Español

1. En conformidad con Frank, se encontró que los errores en magnitud y dirección del vector manifiesto producido por la excentricidad del dipolo son considerables. Sinembargo, estos errores siguen un orden definitivo y los errores que ocurren como resultado de excentricidad del dipolo pueden ser descritos como sistemáticos.

2. Estos errores han sido hallados causar una exageración de la rotación eléctrica del corazón cuando son aplicados al lazo del QRS. Se recalca que la ocurrencia de estos errores sistemáticos no invalidiza las correlaciones hechas en el pasado que empleaban la rotación eléctrica del corazón como un factor. Se sugiere que un entendimiento de los errores de excentricidad pueda hacer posible el entender casos individuales en los cuales la correlación fué pobre.

3. Los complejos mayores que se ven cuando el promedio del eje QRS es +65 a +85 grados y los complejos menores cuando el promedio de QRS esta entre 0 a −30 grados puede ser en parte resultado de la excentricidad.

4. Complejos QRS pequeños en las derivaciones de las extremidades y por consiguiente pequeños, valores del promedio del vector QRS manifiesto, anteriormente atribuidos enteramente a una dirección hacia atrás mayor del promedio espacial QRS, podría ser debido a excentricidad. Se sugiere que esto ofrece una explicación para el hallazgo de potenciales pequeños en la espalda cuando el eje manifiesto QRS es pequeño.

5. Se concluye que la excentricidad de dipolo explica algunos de los lazos "torcidos" y "doblados" registrados por los vectorcardiografos espaciales.

6. Un número de problemas electrocardiográficos individuales aparentaron ceder a análisis por medio de la aplicación de los efectos de excentricidad de dipolo. Unos pocos son descritos.

7. El potencial del terminal central varía considerablemente durante la inscripción del complejo QRS. Esto puede explicar en parte la curiosa división de los lazos de Burch en los dos grupos que el describió. Una correlación con el eje manifiesto QRS se hace.

8. De acuerdo al principio de variación de potencial del terminal central, el valor de cualquier método que emplee derivaciones precordiales "unipolares" para cualquier clase de correlación matemática o para determinar la dirección espacial del eje promedio es dudoso. Junto con otros errores envueltos, esta evidencia hace obvio que tales métodos son delusorios.

También así de acuerdo a este principio la noción de que las derivaciones "unipolares" reflejan el potencial absoluto en algún punto y son así más exactos que las derivaciones bipolares se duda.

Es bastante claro para el autor que el a asumido que el medio de conducción es homogéneo y que es ilimitado. La no homogenidad del medio conductor y los contornos limítrofes de las paredes del tórax, modificaran cuando sus efectos sean conocidos los resultados encontrados en este trabajo. De acuerdo a la opinión del autor estos efectos modificaran los resultados y conclusiones presentados aquí más en una manera cuantitativa que cualitativa.

ACKNOWLEDGMENT

I should like to acknowledge and to express my deepest appreciation for the help of Dr. Richard Ashman in the preparation of this paper.

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REPORT OF COMMITTEE ON ELECTROCARDIOGRAPHY, AMERICAN HEART ASSOCIATION

Recommendations for Standardization of Electrocardiographic and Vectorcardiographic Leads

COMMITTEE MEMBERS: FRANK N. WILSON, M.D., HONORARY CHAIRMAN†
CHARLES E. KOSSMANN, M.D., CHAIRMAN, GEORGE E. BURCH, M.D., EMANUEL GOLDBERGER, M.D., ASHTON GRAYBIEL, Captain, MC, USN, HANS H. HECHT, M.D., FRANKLIN D. JOHNSTON, M.D., EUGENE LEPESCHKIN, M.D., GORDON B. MYERS, M.D.

IT was 16 years ago that the first Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland on the Standardization of Precordial Leads[1] were published. The report, expertly done by selected committees of each of these organizations, was received with considerable enthusiasm by most clinicians, with some misgivings by a few. The latter included those individualists to whom the word standardization is anathema, and to whom conventionalization is synonymous with stultification of thought.

In the years since the report appeared, the concern of the dubious has not been justified. Investigation of new leads and new technics has gone ahead at a good pace. It is doubtful that the standardization has inhibited any investigator from continuing his search for the truth by whatever electrocardiographic method he pleases to use.

On the other side of the question, the mutual agreement on technics and nomenclature has greatly facilitated the clinical use of the electrocardiographic method. Certainly before 1938 the state of precordial leads was chaotic so far as the average practitioner of medicine was concerned. The standardization helped bring a surprising degree of order out of the confusion to the gratification and benefit of physicians and patients alike. It undoubtedly led to many systematic electrocardiographic studies, especially during World War II, which may never have been undertaken or which would not have been easy to compare with other studies by reason of widely varying technics of recording.

The standardization was not meant to be rigid and unchanging as witness the two supplementary reports on precordial leads[2] and the report on electrocardiographic nomenclature[3] of the American Heart Association, a report on multiple unipolar leads by a committee of the British Cardiac Society,[4] and the Recommendations Concerning the Use of Precordial Leads of the German Society for the Study of the Circulation.[5] More recently the fifth edition of the Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels[6] has come off the press. Most of the electrocardiographic section concerned with instruments, technics, and nomenclature, composed by a committee of the New York Heart Association, has been incorporated in the present report. Nevertheless it seemed that the time had come to review the entire subject again, to include vectorcardiography, and to make such recommendations as might seem appropriate in the light of new knowledge and recent additions to old knowledge. Toward this end the present Committee on Electrocardiography of the American Heart Association, after a careful consideration of all of the facts available to it, submits the following recommendations. It will be evident that it has borrowed generously from the excellent reports of previous committees assigned a similar task, and that it has attempted, for obvious reasons, to consolidate all

† Deceased.

previous publications of a similar kind into a single communication.

Electrocardiographic Leads

A. *Instruments**

1. Electrocardiographs shall be equipped with a suitable mechanism for making permanent records.

2. The recorded response of the electrocardiograph to externally applied voltages shall be adjustable to a sensitivity of 1 cm. per millivolt when this voltage is applied to the leads of the instrument through a series resistance of 2000 ohms. This sensitivity shall be maintained without further adjustment within ±5 per cent for a minimum period of three minutes under operating conditions. Operating conditions for the purpose of this requirement are defined as follows: (1) For instruments powered by alternating current at a specified power frequency, the line voltage may vary from 105 to 130 volts and the power frequency ±2 per cent from its specified value. (2) For instruments powered by one or more batteries, the voltage across the terminals of any or all batteries, when under operation, should be between 80 per cent and 100 per cent of their rated voltage.

Under these conditions the response of the instrument to its incorporated standardizing signal of 1 millivolt shall be within ±5 per cent of the response to the externally applied test signal. The instrument shall incorporate means of superimposing its intrinsic test signal upon the cardiographic tracing as recorded from any lead position. It must be possible to apply this signal voltage continuously for a period of two or more seconds.

3. The response of the instrument at 0.2 second after the application of a direct voltage of 1.0 millivolt shall not deviate more than ±10 per cent from the response at 0.04 second. The test voltage of 1 millivolt should be applied to the leads of the instrument through a series resistance of 2000 ohms.

4. When the instrument is adjusted for a maximum deflection of 1 cm. in response to a direct voltage of 1 millivolt, the deflection resulting from a sinusoidal voltage of the same magnitude varying in frequency from 1 cycle to 15 cycles per second shall not be less than 0.9 cm., from 15 to 40 cycles per second shall not be less than 0.8 cm.,† from 5 to 300 cycles per second shall not be more than 1 cm., and from 1 to 5 cycles per second shall not be more than 1.1 cm.

5. When the instrument is adjusted to the sensitivity specified in requirement 2, the recorded response shall be directly proportional to the applied voltage (direct current) within ±5 per cent over the entire recording range.

6. With the two input terminals connected together, a potential difference applied between them and ground should not produce a deflection of more than 1 per cent of that produced by the same potential difference applied between the two input terminals.

7. The instrument shall incorporate a means of continuously recording time intervals on the record, and this must be by means of a device operating independently of the record-driving mechanism. These intervals shall be of 1 second duration or less and the timing device shall be accurate within ±2 per cent. However, a means of superimposing this time signal on the electrocardiographic tracing at the operator's wish will be accepted as fulfilling this requirement. It should be possible to record the time signal for a period of at least two seconds. Recording paper preruled so as to indicate time intervals, assuming a constant paper speed, shall not be construed as fulfilling this requirement.

8. It has become increasingly clear that the more or less standard paper or film speed of 25 mm. per second incorporated in most instruments makes it difficult on occasion to resolve certain diagnostic details of rapid electrocardiographic deflections. It is recommended that multiple speeds be made available, or if

* Modified from a report by the Advisory Committee on Electrocardiographs to the Council on Physical Medicine and Rehabilitation of the American Medical Association.[7]

† The Committee regards these as minimal frequency characteristics applicable principally to portable direct-writing electrocardiographs. Whenever possible the instrument used should have an amplitude response to a sinusoidal voltage considerably in excess of these limits. For a precise study of wave forms, the instrument used should display a flat frequency response from 0.5 to 100 cycles per second as a minimum characteristic.

the instrument provides only one, that this be one of several which the purchaser may select. A speed of 50 mm. per second appears to be particularly useful.

B. Technics

1. *General.* Changes in the electrocardiogram occur in variable degree with change in posture, after meals, after smoking, after exercise and with the use of drugs. The position of the body at the time the recording is made should be stated in the report. The preferred position of the patient is recumbent. The reclining table should be long enough and wide enough to support all extremities. To eliminate shivering, the temperature of the room in which the records are made should be comfortable. For precise, comparative work the patient should be in the basal state at each recording.

2. *Bipolar Extremity Leads (Standard Leads, Bipolar Limb Leads, Standard Bipolar Limb Leads).* Bipolar extremity leads record the difference in potential between two extremities when each is connected to one of the input terminals of the recording device. A lead such as this, in which both electrodes are attached to the body and are relatively equidistant from the heart, is described as bipolar. The difference in potential between the left arm and the right arm is designated as lead I, between the left leg and the right arm as lead II, and between the left leg and the left arm as lead III. In each instance the connections to the galvanometer are to be made in such a way that positivity of the first named extremity with respect to the second results in an upright deflection in the finished record.

In taking these leads the sensitivity of the recording instrument should be so adjusted that introduction of 1 millivolt in the circuit results in a deflection of 1 cm. In practice, this reference voltage or "standardization" should be recorded at the beginning and at the end of each lead.

The electrodes may be placed on any part of the arms or of the left leg in making these leads, so long as they are below the shoulders in the former and below the inguinal fold anteriorly and the gluteal fold posteriorly in the latter. Any other placement of the electrodes made necessary by deformed or missing extremities must be noted on the record. Selection of fleshy rather than bony sites for the electrodes will insure good contacts.

The electrodes may be any of several types provided that a low resistance can be obtained between the surface of the electrode and the skin, and so long as the metal is of low resistance and displays no condenser properties. A convenient electrode used on the extremities is one of German silver, 3.5 cm. by 5.0 cm., which is held in place by an elastic band, and which makes contact with the skin through a conducting jelly. Smaller sizes are preferred for infants.

Electrodes and their contacts with the lead wires of the recording device must be kept scrupulously clean. The entire circuit from patient to machine must be inspected frequently for defects. Unusual care to keep resistance of the skin at a minimum must be used in applying conducting jelly or paste if a single electrode on each limb is to be used for simultaneous recording of bipolar or unipolar potentials of the extremities. If such recording is to be done over an extended period of time, repeated reapplication of the jelly to eliminate drying is necessary. With any type of recording, the electrode jelly must not make contact with the lead cables.

3. *Unipolar Extremity Leads (Unipolar Limb Leads).* The potential of any extremity may be obtained by connecting its electrode (exploring electrode) to one input terminal of the recording device. The other terminal is connected to an indifferent electrode, preferably one with a potential as close as possible to the mean potential of the body during the cardiac cycle. Such an electrode can be constructed by connecting the right arm, the left arm, and the left leg to a central terminal, each through a fixed, noninductive resistance of 5000 or more ohms. It is imperative that the resistances between each extremity and the central terminal be equal. A galvanometric lead in which the central terminal is used as the indifferent electrode is described as unipolar.

Augmentation, whereby the resulting deflections are approximately one and one-half times as large as their true size, may be accom-

plished by severing the connection between the central terminal and the extremity being studied.

In recording the extremity potentials, either in the ordinary unipolar or augmented way, the electrocardiograph is to be so adjusted that a deflection of 1 cm. in the finished record corresponds to a potential difference of 1 millivolt. Any increase in sensitivity of the instrument made necessary by small deflections should be clearly recorded on the curve, preferably at the beginning and at the end of the lead. Connections to the galvanometer are to be made in such a way that relative positivity of the exploring electrode will cause an upright deflection in the electrocardiogram.

When made in the ordinary way the records from the right arm, the left arm, and the left leg are to be designated by the symbols V_R, V_L, and V_F respectively. When the records have been augmented each of these symbols should be preceded by a lower case letter, a, as follows: aV_R, aV_L, aV_F.

4. *Precordial Leads.* The exploring or precordial electrode should be circular and 3 cm. or less in diameter. In children under 10 years of age the diameter should be 1.5 cm. or less. The indifferent or distant contact is to be placed on the central terminal. Leads obtained in this way are designated by the letter V (for voltage) followed by a subscript depending upon the location of the exploring electrode according to the following plan: Subscript 1 shall be used for a lead from the right sternal margin at the fourth intercostal space; subscript 2 for a lead from the left sternal margin at the fourth intercostal space; subscript 4 for a lead from the fifth intercostal space where it is crossed by the midclavicular line; subscript 3 for a lead from a point midway between points 2 and 4; subscript 5 for a lead from the junction of the left anterior axillary line with the horizontal level of position 4. Subscripts 6, 7 and 8 are for leads on the same horizontal level but at the left midaxillary line (6), the left posterior axillary line (7) and the left midscapular line (8), respectively. When additional leads are made from the right side of the thorax, their location is to be indicated by arabic subscripts as for the left side, to be followed by the letter $_R$ (for right). A lead from the fifth intercostal space in the right midclavicular line thus will bear the designation V_{4R}.* If a lead is made from the tip of the ensiform it shall be designated by a lower case e as the subscript, e.g. V_e.

For routine purposes leads should be made from at least three areas widely distributed over the precordium. In this regard the combination of locations 1, 3 and 5 have been found useful, though leads from the first six positions are more informative and, therefore, preferable.

If for any reason the preferred central terminal is not used and instead the right arm, the left arm, the left leg, or a point on the back is the site of the indifferent electrode, the resulting precordial lead is designated as CR, CL, CF, or CB for the respective sites followed by an arabic subscript to indicate the location of the precordial electrode as described above.

In taking unipolar precordial leads, connections to the recording device are to be made as described for the unipolar extremity leads, so that relative positivity of the exploring electrode is represented by an upward deflection in the finished record.

It will be found convenient in taking precordial leads of high voltage to adjust the electrocardiograph so that a deflection of 0.5 cm. in the finished record corresponds to a potential difference of 1 millivolt. The sensitivity should be clearly indicated on the curve by recording at its beginning and at its end the effect of introducing a potential difference of 1 millivolt into the galvanometric circuit.

If large, pendulous breasts are present, it is recommended that these be displaced upward so that as little mammary tissue as possible is between the exploring electrode and the heart.

5. *Unipolar Esophageal Leads.* The exploring or esophageal electrode is preferably a small cylinder, approximately 3 mm. by 4 mm., made of noncorrosive metal. It is connected by insulated wire approximately 100 cm. in length to a clip or jack to which an input terminal of the galvanometer may be attached readily. Several

* By this nomenclature there is no lead V_{2R} or lead V_{1R} because the precordial stations to which they would apply are ordinarily designated as leads V_1 and V_2, respectively.

"ring electrodes" insulated from each other at distances of 2.5 to 5.0 cm. may be arranged along a small bore tube similar to a stomach tube. With this electrode, multiple leads may be made from several esophageal levels without moving the tube.

The depth of an electrode in the esophagus is measured from the anterior nares or the incisor teeth. In adults the exploring electrode is usually close to the heart at levels between 30 cm. and 55 cm. from the reference points. Placement and localization are accomplished best with the aid of a fluoroscope. However, adequate records may be obtained without a fluoroscope if the electrode is placed initially 60 cm. from the reference level. It is then withdrawn gradually in increments of 5 cm. and a record made from each level. If a multiple terminal electrode is available this stepwise procedure is easier to do. The exploring electrode will usually be close to the left atrium when it is 40 cm. from the anterior nares and close to the left ventricle when it is 50 cm. from the anterior nares. These distances are a few centimeters shorter when the incisor teeth are used as a reference level.

The central terminal is to be used as an indifferent electrode as described for other unipolar leads. Response of the electrocardiograph to the introduction of a potential difference of 1 millivolt must be adjusted to the size of the deflections to be recorded, and must be clearly shown on each lead made.

The leads obtained are designated by the symbol V followed by the upper case subscript E and an arabic number to indicate the distance of the electrode from the anterior nares or the incisor teeth, e.g., V_{E23}, V_{E58}.

C. Nomenclature

1. The symbols P, T_P,* QRS, T, and U are to be used to represent the deflections or groups of deflections encountered in the electrocardiogram. Criteria for the use of these symbols apply to all leads, unipolar and bipolar, normal and abnormal.

2. The P wave is normally the gradual initial deflection of any group, and may be a summit or a depression. The level or reference from which its voltage is measured is the isoelectric level (T-P or U-P interval). If it displays turning points on either side of its reference level, it is described as diphasic. If the initial turning point is above this level, it is said to be of the plus-minus (+ −) type, and if below, it is said to be of the minus-plus (− +) type.

In esophageal and intracardiac leads the P wave will usually be composed of multiple rapid deflections not unlike the QRS group of leads from the body surface. It is recommended that the same symbols and criteria of application be used as for the initial ventricular group (see paragraph 5 below) but that the symbol for each atrial deflection be followed by the subscript P, e.g., Q_P, R_P, S_P, R'_P, S'_P, R''_P, S''_P. Further, the level of reference of these deflections, as for the P wave itself, is to be the isoelectric line (T-P or U-P interval).

3. The T_P wave may be found in the P-R segment, that part of the trace between the end of the P wave and the beginning of QRS. It usually continues through the QRS interval. If discernible in leads from the body surface it is a shallow deflection usually below but sometimes above its level of reference, the isoelectric line. In esophageal and intracardiac leads it is often of larger amplitude and may be multiphasic. When there is atrioventricular block, an S-T_P segment preceding and a low summit U_P following the T_P may be identified in such leads.

4. In the majority of electrocardiograms the QRS complex is superimposed on the T_P deflection. For this reason the level of reference from which the voltage of QRS is measured should be at the level at which the first of the QRS components begins. The voltage of an upward QRS deflection is determined by measuring the vertical distance between the upper edge of the trace at the beginning of the QRS interval and the upper edge of the trace at the apex of the deflection. The voltage of a downward deflection is determined by measuring the vertical distance between the lower edge of the trace at the beginning of the QRS interval and the lower edge of the trace at the bottom of the deflection.

5. In order to indicate how the QRS complex

* Formerly T_a.

should be subdivided for the purpose of assigning symbols to its deflections, it should be borne in mind that the first deflection begins at the onset of the QRS interval when the trace first leaves the reference level. From this point the trace rises or falls to a turning point where the direction of its motion is reversed. It may pass through a second and third turning point or even more, causing notches, before crossing to the opposite side of the reference level.* At this crossing the first deflection ends and the second begins. The second deflection, necessarily opposite in direction to the first, must display one turning point and may display many; it does not end until the trace crosses the reference level for the second time. There may be a deflection which begins at the second crossing and ends at the S-T junction. No part of the QRS complex which does not cross the reference level should be considered a separate deflection. If the S-T junction is displaced in a direction opposite to the turning point of the last deflection of QRS, that portion of QRS which lies between this point and the S-T junction should be considered a part of the last deflection.

The earliest QRS deflection which lies above the reference level should be labeled R. Any downward deflection which precedes R should be labeled Q. The first of any downward deflection which may follow R should be labeled S. The first of any upward deflections which may follow S should be labeled R′, and the first of any downward deflections which may follow R′ should be labeled S′. If it is necessary to label still later deflections of the QRS group, the symbols R″, S″, and so on, should be used in accordance with the same principles. When R is absent and the QRS complex consists of a single downward deflection, this deflection should be labeled QS. In statistical studies QS, Q, and S deflections should be considered separately.

* When the trace is descending it crosses the reference level at the instant when its lowest margin reaches a position below that which it occupied at the beginning of the QRS interval. When the trace is ascending it crosses the reference level at the instant when its upper margin reaches a position above that which it occupied at the beginning of the QRS interval.

A deflection is "notched" when it displays more than one turning point on the same side of the reference level. A deflection is "slurred" when it displays a distinct and local thickening on either limb, or at its apex, owing to a sudden and pronounced change in the slope of the curve.

When the form of the QRS complex varies from moment to moment because of the effect of respiratory movements on the position of the heart or for some similar reason, the classification of this complex should be determined by the variety of complex which is most abundant, or, if no type is numerically predominant, by the outline of the complexes which are of intermediate form. Small QRS complexes (largest deflection less than 0.5 millivolt) which display more than three components or multiple slurring and notching should be classed as "small and bizarre" or "vibratory."

In unipolar leads the "intrinsicoid (or RS) deflection" ordinarily begins at the peak of the R wave and ends with the nadir of the S wave. It is usually the steepest and longest downstroke of QRS. In certain precordial leads there may be two R waves (R and R′) and one or two S waves (S and S′). Under these circumstances the longer downstroke is ordinarily regarded as the characteristic one in the lead, although occasionally a shorter but later and more gradually sloping intrinsicoid deflection may have considerable diagnostic significance.

6. The term "S-T junction" or "J" (RS-T junction) should be used to indicate the point or shoulder which marks the end of the QRS complex, the point where the steep slopes of the QRS deflections are more or less abruptly replaced by the more gradual slopes which precede or comprise the first limb of the T wave. In many electrocardiograms the S-T junction is followed by a nearly horizontal or gently sloping segment which lies on, above or below the reference level and ends with the onset of a much steeper slope that rises or falls to the apex of T. The term S-T segment is used for this part of the ventricular complex when it exists, even though electrophysiologically it is the earliest part of the T deflection. When there is no point between the S-T junction and the apex of T at which a sharp change in the

slope of the trace occurs, this part of the ventricular complex should be called the "first limb of the T wave." When the term "S-T segment" is used without reference to some particular electrocardiogram or to some particular class of electrocardiograms, it should be understood to refer merely to that part of the ventricular complex which immediately follows the S-T junction.

The reference level for the measurement of the displacement of the S-T junction (or J) should be the P-R segment at the beginning of QRS. The level of reference for the measurement of the S-T segment, the T wave and the U wave should be the isoelectric level (T-P or U-P interval) when this can be determined; otherwise it should be the level of the trace at the beginning of the QRS interval.

7. The term "diphasic T waves" should be applied to those final ventricular deflections which present two distinct turning points, one on each side of the level of reference, as described for the P waves (see paragraph 2 above).

8. The P-R interval is measured from the beginning of the P wave to the beginning of QRS whether this be represented by a Q wave or an R wave. This interval varies from lead to lead in the same subject. It is recommended that the longest P-R interval found in the bipolar or unipolar extremity leads be regarded as the P-R interval. The longest P-R interval is not necessarily the correct one, but because it does not usually differ from the latter by more than 0.01 second in either direction and because it is easy to measure it is preferred. The most exact approximation to the true P-R interval is obtained by measuring the longest time between the beginning of P and the end of QRS in the six bipolar and unipolar extremity leads, and subtracting from this the longest QRS interval found in these leads. With increased usage of simultaneous recording, significant discrepancies between the "longest P-R interval" and the true P-R interval should be easy to detect.

9. The QRS interval is measured from the beginning (Q or R) to the end of the QRS group of deflections. The longest QRS interval found in the bipolar or unipolar extremity leads is regarded as most nearly correct.

10. The Q-T interval is measured from the beginning of QRS to the end of the T wave. The longest interval found in any lead from the surface of the body is regarded as most nearly correct. Since this interval varies with rate, a correction for this variable must be made in comparative studies.

11. The Q-U interval is measured from the beginning of QRS to the end of U wave. The longest interval found in any lead from the surface of the body is regarded as most nearly correct. Since this interval varies with rate, a correction for this variable must be made in comparative studies.

Vectorcardiographic Leads

A. Instruments

Minimal requirements for acceptable vectorcardiographs employing cathode-ray tubes have not yet been established.

B. Technics

In its present state of development there can be no agreement on the technic to be used in recording vectorcardiograms. Studies of comparative differences are available and convincing, but studies of the comparative value of the various reference systems in use are largely nonexistent at this time. Despite this keenly felt gap in our knowledge, some general agreement on procedure acceptable to physicians and investigators alike will conceivably further rather than retard progress in the field of vectorcardiography just as a standardization of leads promoted clinical progress in precordial electrocardiography a decade and a half ago.

1. *Designation of Axes and Planes.* The objective of using any system of recording vectorcardiograms is to obtain the record in one plane, or to be able to synthesize in a variety of ways its spatial configuration from recordings made in two or more planes. Since all reference systems in use are three-dimensional, a standard designation for the three axes and three planes involved would seem desirable. It is to be noted that such a standardization of desig-

tion in no way fixes the method by which the true record in these planes is obtained. The need for uniformity is accented by the fact that already two different nomenclatures have appeared in the literature.

It is recommended that the three axes of the body—transverse, longitudinal, and sagittal—be designated by the symbols x, y, and z respectively. It is also recommended that the three planes defined by these rectilinear coordinates—the transverse, the frontal, and the sagittal—be designated by the symbols xz, xy, and yz respectively.

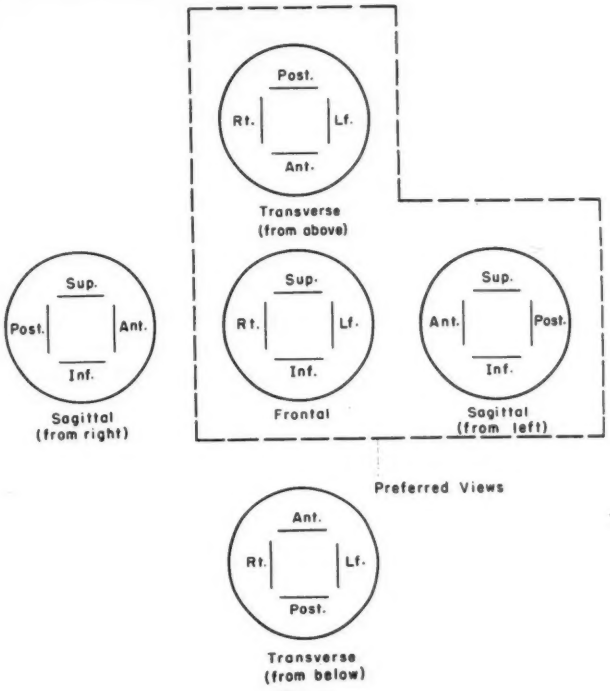

FIG. 1.

2. *Polarity of Leads.* A good deal of misunderstanding exists with regard to the polarity of the leads to be used in any vectorcardiographic reference system. This arises largely from confusion of the direction of motion of the cathode ray when the standardizing voltage is applied with the direction of this motion which results when a voltage obtained from the body is applied.

The conventions to be followed are relatively simple and logical if the source of the cardiac electromotive force is regarded as being a single point. Initially the cardiac vector can only have a direction in three-dimensional space away from this point of zero reference. Under these circumstances the point in question must always be initially electronegative with respect to any other point in the body.

The common method of recording the vectorcardiogram to date is by means of the cathode-ray tube. This tube has four deflection plates, two vertical and two horizontal. When the plates are free of potential the electron beam is in the center of these equidistant and circumferential plates. The "spot" which the beam makes on the face of the tube may be regarded as analogous to the theoretic point source of cardiac potential somewhere in the thorax. To insure correct connections of surface leads in any reference system to the deflection plates it is necessary merely to imagine the screen of the

tube as parallel to the plane of the body (frontal *xy*, sagittal *yz*, or transverse *xz*) being studied, with the observer facing it. The four plates, in the case of the frontal plane, can be divided into superior and inferior, right and left (the right on the observer's left, and the left on the observer's right). In the case of the sagittal plane they are superior and inferior, anterior and posterior, and in the case of the transverse plane they are anterior and posterior, right and left (fig. 1). In any system of *bipolar leads*, pairs of electrodes on the body are attached to pairs of the cathode-ray plates bearing the same relative positions to the respective point sources of potential: the heart in the body, the "spot" on the cathode-ray screen. In *unipolar leads* the exploring electrode is attached to the plate corresponding to the location of the exploring electrode on the body. For example if lead aV_F is regarded as giving the *y* component of the vectorcardiogram, the exploring electrode is attached to the lower plate and the central terminal of Wilson, Macleod and Barker to the upper plate in either the frontal or sagittal displays. If the body is viewed from above, and a point on the back is regarded as yielding the *z* component, the exploring electrode is attached to the posterior plate; but if a point on the front of the chest is used for this component, the exploring electrode is attached to the corresponding anterior plate.

3. *Selection of Views.* In figure 1 it will be seen that there are two views for the transverse and sagittal displays (above or below, left or right). There is also a rear view of the frontal record obtained simply by reversing the connections to the *x*-axis plates. This view is rarely if ever used in vectorcardiography. With regard to transverse and sagittal views, the alternatives in each instance seem to have been used with almost equal frequency by various investigators in the field. Nevertheless, clinical usage would be augmented if only one of the two alternatives for each display were used routinely. Toward this end it is recommended that the preferred views of the spatial vectorcardiogram be from the front, from above, and from the left.

4. *Polarity of Standardizing Voltages.* If the above recommendations on polarity are followed in recording leads, it makes no difference which polarity is used for the standardizing voltages placed across the plates. For uniformity, however, it is suggested that in the individual axes the polarity be arranged so that the direction of planar displacement of the electronic beam in response to the impressed force will be respectively to the left, downward, and backward.

C. Nomenclature

As in the conventional electrocardiogram it is possible to identify portions of the vectorcardiographic trace ascribable to four different electrical processes. These are depolarization and repolarization of the atria and of the ventricles. By the usual methods of recording, the tracings of these processes overlap on the face of the cathode-ray tube. However it is possible to separate them one from the other by electronic and photographic selection. The exception is that part of the trace caused by repolarization of atrial muscle, the terminal portion of which is normally obscured by the simultaneous occurrence of ventricular depolarization. However, even this part of the trace may be distinctive if there is prolonged or blocked atrioventricular conduction.

It is recommended that the four components of the vectorcardiogram be designated as "forms" or "loops" and that the letters P, T_P, QRS, and T, be used to describe the four forms ascribable to the same electrical processes which account for the similarly designated deflections in the conventional electrocardiogram. If an after-potential form can be identified, it is recommended that this be called the U form.

Since an abbreviation or symbol for the word "vectorcardiogram" will clearly be useful, it is suggested that this be VCG.

The Committee discussed other aspects of nomenclature in vectorcardiography, but opinions varied so widely it was concluded not to make further recommendations at this time.

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CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

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Unusual Forms of Heart Disease

By HOWARD B. BURCHELL, M.D.

I AM in general accord with Hutchison's "Don'ts for Diagnosticians," the first two of which read, "Don't be too clever" and "Don't diagnose rarities." Hutchison[1] himself quoted Samuel Gee, who said, "Common things most commonly occur," and it may be emphasized that many rare cardiac conditions perhaps could be all but forgotten, without loss, in day-to-day cardiologic practice. Unusual manifestations of common diseases probably mislead the physician more often than do unusual diseases. Rare conditions tend to be the spice of practice, however, and constitute the substratum whereon one's probing wits are tested. To a certain extent, also, missing of the diagnosis of a rarity is the *bête noir* of the specialist.

Moreover, in this era of rapid transportation, the patient who has sought diagnosis without success often travels far looking for special help. Thus, by force of numbers, a rarity becomes less an event in a large institution than in general practice. This fact is well known and is well exemplified in the discussions of consultants who participate in the "Weekly Clinicopathological Conferences" based on "Case Records of the Massachusetts General Hospital" and reported in *The New England Journal of Medicine*. Some readers of these reports, whose native language is other than English, must be perplexed by the high incidence of symptoms and signs which are designated as possible "red herrings." And the mystification of such foreign visitors would be fully as deep if they were present when one or another of us, under the duress of a similar conference, became, and was called, "as independent as a hog on ice."[2]

In cardiac clinicopathologic conferences which I attend, of the difficult cases chosen for presentation, some are selected because the diagnosis originally was missed, partly or entirely. We believe there is no "news leak"; nevertheless, by the time the clinical part of the conference is over, at least three-fourths of the cases are accurately assessed. Thus, in our clinic at least, if patients who constitute diagnostic enigmas could be tagged at the time of registration, "Potential Conference Material," and if they could appear at one of the clinicopathologic conferences, the diagnostic accuracy of the consultants would increase several fold.

The unusual cases wherein the cardiologist might be at a loss for a diagnosis may be classified as follows: (a) rare anatomic conditions, for example, Ebstein's malformation of the tricuspid valve, traumatic rupture of a valve, primary neoplasm; (b) heart affected as an integral part of a general disease, for example, amyloidosis, lupus erythematosus, scleroderma, hemochromatosis; (c) cardiac complications of other disease, for example, diphtheria, purulent pericarditis, sickle cell and other anemias, thyrotoxicosis both overt and occult, arteriovenous fistula, myocardial metastasis; (d) conditions precipitating or accelerating the development of more usual forms of acquired heart disease, for example, xanthomatosis, possibly obesity, myxedema; (e) conditions mimicking primary heart disease, for example, thrombosis or involvement of the inferior vena cava by tumor.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

A paper given before the San Francisco Heart Association Postgraduate Symposium, October, 1953, with minor abridgments and editorial revisions for which the author acknowledges the help of Dr. Richard M. Hewitt, of the Section of Publications.

The foregoing classification could be followed in this presentation although there are many other approaches. A somewhat frantic person, searching for novelty, might write "A Cardiologist's ABC of Rarities," thus: A is for amyloid, B for beriberi; C is for contusion, D for diphtheria; E is for Ebstein's, F for Fiedler's; G is for glycogen storage, H for hemochromatosis, and so on. For the privilege of being represented by certain of the letters, there would be competition among several conditions. Rare conditions would come to mind to correspond with every letter except J and Z. That approach admittedly is childish but, since it has been made, it could be followed out, spottily, in rhyme:

Don't fail to note, in amyloid
Abundant syndromes are deployed;

And always with a heart contusion
Arise both doubt and much confusion.

The palsy of diphtheria
Must not be thought hysteria.

In hemochromatosis we
Demand hepatic biopsy.

That, I hope, Dr. Bett[3] would admit as "judicious levity." At all events it is not entire nonsense and what follows is serious. In any complete listing of abnormal cardiac conditions, many would fall into the category of controversial states. The question whether some of them actually exist often would have to be answered: "Perhaps," or "Perhaps; probably." To many other questions positive answers cannot be given; here are some of the questions: Can a thyroid nodule be responsible for auricular fibrillation in the absence of signs of hyperthyroidism? Can auricular fibrillation, which is present for many years, of itself result in heart failure or cardiac enlargement? What are the basic faults in conditions called presbycardia or kyphoscoliotic heart disease (without pulmonary disease)? Could there be a basic physiologic and anatomic defect in the form of anxiety neurosis, still frequently termed "neurocirculatory asthenia"?

The first condition on the alphabetical list is amyloidosis. This is not a particularly rare condition; I see several cases a year. It appears in either a primary or a secondary form. In the former the heart is often seriously affected and heart failure is the predominant feature. Primary amyloidosis may be chiefly manifest in any of many organs or tissues, particularly in the heart, liver, kidneys and peripheral nerves. The similarity of the picture to that of chronic constrictive pericarditis has been emphasized and, in the two conditions, the same type of curve of abnormal filling of the ventricle may be seen.[4] In the presence of disease of many organs the diagnosis of primary amyloidosis should be particularly considered. The diagnosis is best confirmed by needle biopsy of the liver. Some of the problems encountered when a patient presents himself with the disease were represented in a clinical conference recently arranged by Pruitt, Daugherty and Edwards.[5]

The term "amyloid," from the Greek word for "starch," was coined because of the avidity with which the abnormal substance takes up iodine, as does starch. This property aroused in Hanson and McConahey,[6] of our clinic, the hope that a tracer study with radioiodine would be diagnostically useful. Their hope has been substantiated in an occasional case but not in others. In two of four cases the extrathyroidal disposal rate was high, and in one of these radioactivity over the liver and spleen was increased.

Even secondary amyloidosis, although sparing the heart, may not necessarily spare the heart specialist of a consultation. A case in point (and it may be used as the basis of a plea against too early and too rigid subspecialization) is the following:

A middle-aged man complained of abdominal pain and diarrhea of two years' duration. In addition, he had lost weight, was weak and his legs were edematous. Because of the last, a cardiologist was asked to see the patient. The primary diagnoses were regional ileitis, ileocolic fistula and possibly pelvic abscess. Surgical operation was necessary in any event. In spite of appropriate treatment, however, the patient died on the second day after operation, with azotemia and in shock. On postmortem examination, amyloidosis, mainly of the kidneys and adrenal glands, was found. It is of interest that these diagnoses were tentatively made in the clinicopathologic conference, before the postmortem diagnosis was disclosed.

In my "ABC of Rarities," under B is found beriberi. In the northern Mississippi Valley, this condition is rare indeed. In spite of our suspicions when individuals, particularly alcoholics, present unusual types of heart failure, I believe there has not been a single established case of beriberi heart failure in a Rochester hospital in the past 10 years.

Another disease in association with which heart failure may be the presenting symptom is hemochromatosis. In about a fifth of the 13 cases in which the diagnosis has been made in our clinic, heart failure has been present. The quantity of pigment in the myocardium at times has seemed sufficient to be responsible for the heart failure. However, other contributing factors, such as coronary disease accelerated by the diabetic state, or possibly anemia from bleeding esophageal varices, must be suspected.

In an early paragraph of this article unusual cases in which the cardiologist might be at a loss for a diagnosis were classified. The conditions just discussed were in the second category of that classification; that is, the heart was affected as part of the general disease. The first category of the classification included rare anatomic conditions and here, as an example, I have chosen Ebstein's malformation of the tricuspid valve. At the clinic we now have recognized nine cases. In this condition, the ability of the right ventricle to impel an adequate quantity of blood into the lungs is impaired by reason of a misplaced, deformed tricuspid valve. Sometimes there is tricuspid insufficiency, sometimes not. The characteristics of the syndrome are varying cardiac enlargement, clear lung fields and low pressure in the right side of the heart as determined by cardiac catheterization. The electrocardiogram not infrequently gives evidence of right bundle-branch block. In the majority of the cases there is an associated atrial septal defect, which allows a right-to-left shunt, and resulting mild to moderate cyanosis. If the patient is seen before heart failure has entered the situation and the shunt is copious, closure of the atrial septal defect may be considered. In Rochester this was done in one case and the patient, who previously had been nearly an invalid, has been able to lead a normal, active life. After the operation, arterial oxygen saturation became normal. Sometime in the future heart failure may develop, but, from the point of view of amelioration of the condition, the operation has been an outstanding success.

In passing, mention may be made of one congenital condition which, previously thought to be rare, is now recognized as relatively common. This is isolated pulmonary stenosis, perhaps more properly called "pulmonary stenosis with intact ventricular septum." In some cases there is obvious, or gross, shunting of venous blood through atrial septal defects; in others, the shunt is minimal and is demonstrable only by special technics, such as central injection of dye; in some, the shunt may be considered only potential; in still others, the shunt is left-to-right through an atrial septal defect; finally, in some cases the atrial septum is intact and no shunting of blood is possible.

Among anatomic rarities, the cardiac and vascular defects associated with Marfan's syndrome and the syndrome associated with anomalous origin of the left coronary artery from the pulmonary artery should be remembered. Another anomaly, one in which surgical measures may be lifesaving, is a form of obstruction to venous outflow from the lungs; it thus simulates mitral stenosis, and is called "cor triatriatum." Edwards and I[7] believe the condition is related to congenital stenosis of a common pulmonary vein. Our patient was an infant, but in Borst's[8] case the patient lived to adulthood and, incidentally, the auscultatory findings were those of mitral stenosis.

To depart from the order of the classification, other conditions that have simulated mitral stenosis are worthy of mention. Such conditions are acquired stenosis of the pulmonary veins[9] and left atrial tumor.[10] The case of the former condition with which I am familiar is believed to be particularly pertinent to the pathogenesis of arterial lesions of the lung, because the arterial lesions were predominantly in the lobes which corresponded with the more marked venous obstructions. The left atrial tumors which I have in mind are polypoid masses which usually are designated as myxomas. But some of these masses might be considered, by some pathologists, not to be

true tumors but organized thrombi. That the one can mimic the other is unquestionable. Particularly in the presence of a normal mitral valve, however, a cellular mass with a stalk, accompanied by deep disruption of the atrial wall, is a tumor, both in my opinion and in that of Pritchard,[11] who studied a large series.

In a number of cardiac states a patient's condition may suddenly change. Among these states are spontaneous rupture of valves, of chordae tendinae, or of aortic sinus aneurysms. It is considered best not to use the word "spontaneous" in relation to that type of rupture of chordae tendinae which occurs after myocardial infarction. In one case of mitral insufficiency reported by Becker, Edwards and me,[12] the date of rupture seemed established and the patient lived approximately a year. Within this type pulmonary arterial changes developed.

Edwards[13] mentioned another most unusual case of corrected complete transposition of the great vessels in which the left atrioventricular valve simulated the tricuspid valve and was insufficient.

Aortic sinus aneurysms frequently rupture into the right side of the heart and a continuous bruit, like that of patent ductus arteriosus, results. The sudden onset of weakness or dyspnea coincident with the appearance of such a bruit is clinically diagnostic. Substantiation may be had from cardiac catheterization, whereby arterial blood is obtained from the right atrium or ventricle. Aneurysms usually are in either the right anterior or the posterior aortic sinus. Those in the former situation not infrequently are associated with a ventricular septal defect. When rupture in this area occurs, it is into the outflow tract of the right ventricle, whereas lesions in the posterior aortic cusp rupture into the right atrium. As a corollary, when "arterialization" is found in the right atrium, the lesion, as compared with an anterior one, should be more amenable to surgical treatment, either from the atrial or the aortic side, because it could be more easily located and its origin would not be associated with the origin of a coronary artery; the posterior aortic cusp is the "noncoronary" one. It is well to emphasize that a rupture with a remarkably small orifice (2 to 3 mm.) may give rise to heart failure in this condition. Kirklin[14] has unsuccessfully attempted to close one such rupture of a posterior aortic cusp aneurysm through a right atrial approach.

Idiopathic pulmonary hypertension remains an enigma from the etiologic viewpoint. At present, its rapid course makes it seem unlikely that it bears any direct etiologic relationship to systemic primary hypertension. If primary pulmonary hypertension ever is akin to the systemic type, it very rarely is so. When severe pulmonary hypertension develops, whether from pulmonary arterial lesion including emboli, or perchance from primary pulmonary hypertension, and right heart failure ensues, there may develop a cyanotic condition related to functional opening of a foramen ovale. This condition has been seen at the clinic on a number of occasions and, by the dye indicator method, the site of a right-to-left atrial shunt clearly has been demonstrated.[15]

The term, "idiopathic acute pericarditis" and the condition it denotes may be regarded as relatively commonplace. It is important to emphasize, however, that diagnostically, the term is indefinite. It is well, always, to consider etiologic possibilities and, if reversion to health or of the cardiac silhouette to normal size is delayed, pericardial biopsy should be considered. By such a measure granulomatous or neoplastic disease may be discovered in time to allow appropriate management to be instituted.

Occasionally heart failure is related to systemic arteriovenous fistula. The last case of this sort encountered in Rochester was that of a young man who was referred there because he was in desperate straits from the effects of a fistula involving the aorta and inferior vena cava, which had been recognized following operation for a protruded lumbar disk. Kirklin[14] successfully performed aortic graft and the patient has returned to normal health. Since the report of Edholm and associates[16] on heart failure in association with Paget's disease, cases of this disease have been observed at the clinic in which there was a high normal cardiac output, but in none of the cases was the heart failing. In one case in

which Paget's disease was markedly localized to one tibia, there was found arterialization in the femoral vein, as compared with that in the contralateral limb, and a slight bradycardic response was elicited on digitally occluding the femoral artery.

A common noncardiac condition that not infrequently is treated as a heart condition is emphysema. Although heart failure may be an associated condition, such association is uncommon. There are certain obese, middle-aged women with lipedema, whose fluid balance markedly and rapidly varies, sometimes with menstrual cyclic changes. Although one patient in this category is seen every month or so, and gives a convincing story of marked diuresis following administration of a mercurial diuretic, not one has had significant edema at the time of my consultation.

A rare condition superficially suggesting heart disease is that related to a renal tumor, with invasion and obstruction of the inferior vena cava. One of these cases is found each year or so at the clinic. It is possible for death to occur from a huge pulmonary embolus consisting of tumor tissue. Occasionally cases of phlebothrombosis of the lower extremities may be transiently suspected of being cases of heart failure. In this connection it is worth reemphasizing that apparently idiopathic venous thrombosis carries a high correlation with neoplastic disease, particularly with that of the pancreas. Absence of cervical venous engorgement practically should exclude heart disease as the underlying cause of edema of the leg related to obstruction of the inferior vena; yet it is remarkable how often this simple sign is not sought. Even in the reverse situation—that is, when cervical venous engorgement is present and crying for recognition—it may be disregarded for a long time. Consequently, chronic constrictive pericarditis may be labeled, erroneously, portal cirrhosis.

In spite of many advances in knowledge of heart disease, patients who come to the physician with symptoms of circulatory deficiency and enlarged hearts, may improve, depart, and diagnosis never may be established in their cases, not even by the regrettable method of postmortem examination. It is easy to label such cases rheumatic or viral myocarditis, but there is an intellectual dissatisfaction in complete acceptance of such diagnoses. Viral myocarditis as an entity is well established but certainly is a rarity, difficult of exact etiologic substantiation and difficult of assessment as regards the amount of histologic change to correlate with the clinical picture.

Much is left untouched in this survey of the cardiologist's role in recognition of the unusual syndromes with which he may be confronted. For instance, the whole field of unusual electrocardiograms has not been entered because, although they are important, it is only occasionally that they are related directly to the patient's presenting symptoms. Clinical practice often gives evidence of the truth of the old adage that to think of a rarity is practically to exclude it. Particularly in teaching institutions, and especially in the early years of teaching, an unusual problem offers a temptation to adopt desperate measures in the attempt to obtain a diagnosis. It is best sometimes to leave the diagnosis indeterminate, particularly when tests that might be employed entail danger or worrisome expense and cannot lead to definitive treatment. As Jeans has been quoted as saying: "A living problem is better than a dead certainty."[17]

An ABCD of rarities ought to end with W, X, Y, Z. This one can so end if W is allowed to stand for work hypertrophy, X for xanthomatosis, Y for yellow fever heart, and Z for zootomic hearts. Then, with some license as to stressed syllables, the following so-called couplets emerge:

Work hypertrophy may have been found
In coolies pulling jinrickshas round.

A precocious status anginosis
Is one that's called xanthomatosis.

An evil virus, at least in part,
Is the cause of yellow fever heart.

Last come the strange zootomic hearts,
Not known or seen within these parts.

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AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM OF THE EIGHTH ANNUAL MEETING, TO BE HELD AT THE SHERATON HOTEL IN CHICAGO, ILL., OCTOBER 31, TO NOVEMBER 1, 1954

(All papers except the Addresses will be limited to 15 minutes for presentation plus 5 minutes for discussion)

OCTOBER 31, 1954

Russell L. Holman, Presiding

8:15
REGISTRATION

9:00
1. A PROCEDURE TO AID IN THE EVALUATION OF PERIPHERAL CIRCULATORY FUNCTION IN OLDER SUBJECTS. M. Landowne, F. Silverstone and H. M. Silver.

9:20
2. THE SERUM PHOSPHATIDES IN HEALTH AND IN DISEASE. M. M. Gertler, J. Kream and B. S. Oppenheimer.

9:40
3. AN EVALUATION OF THE BLOOD LIPIDS IN HUMAN ATHEROSCLEROSIS: A PRELIMINARY REPORT. J. C. Paterson, B. Cornish and E. C. Armstrong.

10:00
4. SERUM LIPIDS IN CAREFULLY SELECTED "ATHEROSCLEROTIC" AND "NORMAL" MALES. J. A. Little, H. M. Shanoff, R. W. Vander Flier and H. E. Rykert

10:20
RECESS

10:30
5. A SERUM LIPOPROTEIN PATTERN CHARACTERISTIC OF BILIARY OBSTRUCTION, WITH SOME COMMENTS ON "JAUNDICE DUE TO METHYLTESTOSTERONE." R. H. Furman, L. L. Conrad and R. P. Howard.

10:50
6. FIRST INTERIM REPORT ON THE EFFECTS OF ESTROGEN THERAPY IN MALES UNDER 50 YEARS OF AGE WITH A PREVIOUS SINGLE MYOCARDIAL INFARCTION. J. Stamler, R. Pick and L. N. Katz.

11:10
7. EFFECTS OF LONG-TERM ESTROGEN AND HEPARIN ADMINISTRATION ON SERUM LIPOPROTEIN LEVELS IN HYPERCHOLESTEROLEMIC HUMANS, E. Boyle.

11:30
8. AN EVALUATION OF THE EFFECT OF CHOLINE AND INOSITOL ON THE CLINICAL COURSE AND SERUM LIPIDS IN PATIENTS WITH AGNINA PECTORIS. R. S. Jackson, C. F. Wilkinson, L. Meyers, M. S. Bruno and M. R. Benjamin.

11:50
9. THE PRODUCTION OF CARDIOVASCULAR DAMAGE IN YOUNG RATS BY A DIETARY DEFICIENCY OF LIPOTROPIC FACTORS. W. S. Hartroft.

12:30
LUNCHEON:
INVITATIONAL ADDRESS: "CARDIOVASCULAR CONCEPTS: THE PAST FIFTY YEARS," by Carl J. Wiggers, M.D., D.Sc., Honorary Professor of Physiology of the Frank E. Bunts Educational Institute, Cleveland Clinic Foundation and Emeritus Professor

of Physiology, Western Reserve University, Cleveland, Ohio.

2:00
BUSINESS MEETING

2:20
PRESIDENTIAL ADDRESS: Dr. Russell L. Holman, "PATHOGENESIS IN ATHEROSCLEROSIS."

Louis N. Katz, Presiding

2:40
10. ABSORBABILITY OF DIHYDROCHOLESTEROL AND SITOSTEROL. R. G. Gould.

3:00
11. THE SERUM CHOLESTEROL LEVEL AND LIPOPROTEIN PATTERN FOLLOWING THE ADMINISTRATION OF PLANT STEROLS. C. R. Joyner and P. T. Kuo.

3:20
RECESS

3:30
12. EFFECTS OF PROLONGED ADMINISTRATION OF SITOSTEROL ON SERUM LIPIDS. M. M. Best, C. H. Duncan, J. D. Wathen, E. J. VanLoon and R. E. Shipley.

3:50
13. STUDIES OF NORMAL ENDOGENOUS LIPEMIA CLEARING FACTOR. H. Engelberg.

4:10
14. EFFECTS OF HEPARIN ON THE DEVELOPMENT OF ATHEROSCLEROSIS AND OF FATTY LIVER IN CHOLESTEROL-FED RABBITS. H. C. Meng and W. S. Davis.

4:30
15. HEPARIN-LIKE ACTIVITY OF POLYMETAPHOSPHATE. R. J. Havel and J. H. Bragdon.

4:50
16. STUDIES ON CLEARING FACTOR, A. LIPOPROTEIN LIPASE. E. D. Korn.

6:00–7:00
COCKTAILS

NOVEMBER 1, 1954

L. L. Waters, Presiding

8:30
REGISTRATION

9:00
17. PRODUCTION OF ATHEROSCLEROSIS IN THE RAT, AN OMNIVOROUS MAMMAL, BY FORCED FEEDING OF VEGETABLE OIL: PRELIMINARY REPORT. M. R. Malinow, D. Hojman and A. A. Pellegrino.

9:20
18. PRODUCTION OF HYPERLIPEMIA AND LIPOID INFILTRATION OF INTIMA AND MEDIA OF AORTA BY A HIGH FAT, CHOLESTEROL FREE DIET. A. Steiner and S. Dayton.

9:40
19. THE EFFECTS OF CERTAIN VEGETABLE AND ANIMAL FATS ON PLASMA LIPIDS OF HUMANS. J. M. R. Beveridge, W. F. Connell, G Mayer, J. B. Firstbrook and M. DeWolfe.

10:00
20. FURTHER EXPERIENCE WITH HIGH VEGETABLE FAT DIET IN PATIENTS WITH EXTENSIVE DIABETIC VASCULAR DISEASE. L. W. Kinsell, G. C. Cochrane, S. Smyrl, G. Fukayama and M. Coelho.

10:20
RECESS

10:30
21. THE BIOSYNTHESIS OF CHOLESTEROL AND ITS ACCUMULATION BY THE WHOLE AORTA MAINTAINED IN VITRO. N. T. Werthessen.

10:50
22. AORTIC SYNTHESIS OF PHOSPHOLIPIDS IN EXPERIMENTAL RABBIT ATHEROMATOSIS.

M. L. Shore, D. B. Zilversmit and R. F. Ackerman.

11:10

23. Rates of Acetate Turnover and Lipid Synthesis in Normal, Hypothyroid, and Hyperthyroid Rats. S. Dayton, J. Dayton, F. Drimmer and F. E. Kendall.

11:30

24. Uptake of Radioactive Sulfur by Vascular Tissue. R. C. Buck.

11:50

25. Immunochemical Relationship of the Protein Moieties of Human Plasma β-Lipoprotein and Chylomicrons. E. Middleton.

A. C. Corcoran, Presiding

2:00

26. Blood Chemical Studies in Depancreatized Rabbits on Various Diets. O. J. Pollak, W. G. Chubaty, I. R. Mazer and J. S. Evans.

2:20

27. The Rate of Regression of Hypercholesteremia and Atherosclerosis in Chicks: Effects of Diet, Pancreatectomy, Estrogens and Thyroid. S. Rodbard, R. Pick and L. N. Katz.

2:40

28. Transient Hyperlipemia and Atherogenesis in Rabbits Following the Intravenous Injection of Colloidal Solutions. E. V. Lautsch, G. C. McMillan and G. Lyman Duff.

3:00

29. Tissue Permeability: A Factor in Experimental Atherosclerosis. Studies with Cortisone and Hyaluronidase. Chun-I Wang, L. E. Schaefer and D. Adlersberg.

3:20

Recess

3:30

30. Morphogenesis of Atherosclerosis in Swine Aortas. H. L. Gottlieb.

3:50

31. Observations on the Metabolism of Cholesterol-4-C^{14} in the Dog. E. H. Mosbach and L. L. Abell.

4:10

32. In Vitro Production of Atheromata. W. C. Felch, L. B. Dotti and D. J. Reisner.

4:30

33. A Preliminary Report on the Prevention of Necrotizing Arteritis in Dogs by B Complex Vitamins and a Possible Interpretation. J. C. Geer and R. L. Holman.

TO BE READ BY TITLE

34. Genetic Aspects of Idiopathic Hypercholesteremia: Studies of Parents and Offspring in 200 Randomly Selected Families. D. Adlersberg, L. E. Schaefer, A. G. Steinberg and Chun-I Wang.

35. Approaches to a Therapy of Arteriosclerosis. R. Altschul.

36. Lipoprotein Profiles in Normal and Pathologic States: Comparative Paper-Electrophoretic Studies in Man and Other Mammals. E. T. Bossak, Chun-I Wang and D. Adlersberg.

37. The Production of Cardiac and Vascular Lesions by Feeding Deficient Diets. D. H. Copeland, W. D. Salmon and M. J. Burns.

38. Hypercholesterolemia in Monkeys Ingesting an Adequate Diet. G. E. Cox, L. G. Nelson and C. B. Taylor.

39. The in Vitro Exchange of Phospholipid Phosphorus between Lipoproteins. H. A. Eder, J. H. Bragdon and E. Boyle.

40. Atherosclerosis in the Intramural as Compared to Extramural Coronary Arteries. J. C. Edwards.

41. Studies of Arteriovenous Oxygen Differences in Atherosclerotic Individuals before and after Heparin. H. Engelberg and R. Kuhn.

42. Correlation of Plasma Heparin Levels and Serum Low Density Lipoproteins. H. Engelberg.

43. Newer Clinical and Laboratory Studies in the Aged. IV. Atherosclerosis in Normal Patients 80–100 Years of Age. A. A. Goldbloom, H. B. Eiber, I. Chapman, O. Deutschberger and W. R. Loewe.

44. Postmortem Studies of Serum Lipoproteins in 100 Consecutive Autopsies. I. J. Greenblatt, V. A. Bradess and D. M. Spain.

45. The Effect of Brain Extract on Endogenous Hypercholesteremia. R. J. Jones, E. L. Balter and S. Huffman.

46. Field Studies in Italy, 1954, on Serum Cholesterol and Lipoproteins, Coronary Heart Disease and the Diet. A. Keys, F. Fidanza, P. D. White, B. Swahn and M. H. Keys.

47. The Presence of Succinic Dehydrogenase and of Krebs' Cycle Enzymes in Human Aortic Tissue. J. E. Kirk and T. J. S. Laursen.

48. Changes with Age in Diffusion Coefficients of Solutes for Human Aortic Tissue. J. E. Kirk and T. S. Laursen.

49. The Interpretation of Tests of Peripheral Circulatory Function. M. Landowne.

50. Low-Density Lipoproteins Versus Serum Cholesterol in Familial Hypercholesterolemia. L. A. Lewis, A. C. Corcoran and I. H. Page.

51. Spontaneous Arteriosclerosis in Epinephrine-Thyroxine and in Cholesterol Induced Arteriopathy. Y. T. Oester, O. F. Davis and B. Friedman.

52. The Demonstration of Iron in Early Atherosclerotic Plaques. J. C. Paterson and T. Moffatt.

53. Influences of Neutral Fat and Plant Sterols on Exogenous and Endogenous Hypercholesterolemia and Hyperphospholipemia in Chicks. R. Pick, L. N. Katz, S. Rodbard and J. Stamler.

54. Four Years Preliminary Review Clinic for the Study of Arteriosclerosis. P. B. Roen, E. W. Townsend and J. W. Perry.

55. The Relationship of Essential Hyperlipemia to Premature Atherosclerosis. A. Soffer and M. Murray.

56. Hemorrhagic Lipemia and the Production of Clearing Factor in Rabbits. J. J. Spitzer.

57. Dietary and Hormonal Influences on Hepatic Cholesterol Synthesis in Chicks. J. Stamler, R. G. Gould and C. B. Williams.

58. Atherosclerosis in Areas of Vascular Injury in Monkeys with Mild Hypercholesterolemia. C. B. Taylor, G. E. Cox, B. J. Hall-Taylor, and L. G. Nelson.

59. Serum Cholesterol Concentration and Ballistocardiographic Characteristics of Middle-aged Men. H. L. Taylor and J. T. Anderson.

60. Plasma Lipids and the Arterial Wall. L. L. Waters.

61. Atheromatous Hypertension—A Clinical Entity. Diagnosis and Management. J. B. Wolffe.

62. The Phospholipids of the Plasma Lipoproteins. J. M. Steele, H. J. Kayden, B. B. Levy and H. Appleton.

63. Femoral Arteriography in Arteriosclerosis Obliterans. C. M. Greenwald, F. A. LeFevre and V. G. deWolfe.

PROCEEDINGS OF THE EIGHTH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ABSTRACTS

1. A Procedure to Aid in the Evaluation of Peripheral Circulatory Function in Older Subjects

Milton Landowne, Felix Silverstone and Harold M. Silver

Section on Gerontology, National Heart Instutite, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare, Bethesda, and the Baltimore City Hospitals, Baltimore, Md.

A study of skin temperature responses to the indirect vasodilatation induced by heating the trunk was undertaken to obtain normative data which may be useful in practical clinical evaluation, particularly of the older individual. The design of the study considered test acceptability, safety and convenience as well as reproducibility and interpretability. Duplicate satisfactory tests were obtained under standardized environmental conditions.

Illustrative are data for toe temperature of 78 males 26 to 92 years old (mean 58), selected as presenting neither history nor symptoms suggestive of peripheral circulatory impairment. On the basis of careful clinical examinations, 12 were graded functionally as class II and the remainder as class I.

The average maximal toe temperature reached was 30.7 ± 3.6 C. Of the 38 subjects who were less than the mean age, 34 attained a higher than mean toe temperature. Two of these were class II. Seventeen older subjects behaved similarly. In the remaining 23 older subjects, toe temperature did not exceed 30 C. Of the 10 older subjects in class II, only one showed a rise to over 30 C.

Eight additional subjects with clinically demonstrable peripheral vascular disorders were also tested. In none did toe temperatures attain 30 C., and in only two was 25 C. exceeded.

The response to this maneuver in *some* subjects who show no evidence of disordered circulation is thus similar to that characterizing subjects who are suspected of limitation in reserve, and it is no greater than the response of some patients with manifest disease. The procedure, interpreted with caution, is a useful screening aid for possible functional impairment in the abscence of clinical history, symptoms or signs of a disorder of the peripheral circulation. It is advocated to support, and not to replace or detract from, careful clinical evaluation.

2. The Serum Phosphatides in Health and in Disease

M. M. Gertler, J. Kream and B. S. Oppenheimer

Mt. Sinai Hospital, New York, N. Y.

In recent years an etiologic relationship has been suggested between serum phosphatides (phospholipids) and atherosclerosis.

Since the phosphatides found in serum are chemically heterogeneous, it was felt that valuable contributions to the above problem would be made if one attempted to study pathologic changes in phosphatide composition rather than changes in total content as implied by mere lipid phosphorus determinations.

Therefore, methods have been developed in our laboratory (Gertler, M. M., Kream, J. and Baturay, O.: J. Biol. Chem. **207:** 165, 1954) which enable one to analyze small samples of blood serum for their contents of choline, serine, and ethanolamine containing phosphatides respectively.

The method basically consists of (a) extraction and hydrolysis of the serum phosphatide fraction, and (b) separation and quantitative estimation of the nitrogenous components (choline, serine and ethanolamine) by paper partition chromatography and quantitative colorimetry respectively.

Data will be presented from a population of (a) normal males, (b) normal females, (c) pregnant women at various stages of gestation, (d) males with coronary heart disease, and (e) umbilical cord blood. In addition to these studies data will be presented showing the differential change of serum phosphatides during administration of (a) estrogens and (b) lipotropic agents.

Interesting data have accumulated from these investigations. Phosphatides containing choline (for example, lecithin and sphingomyelin) appear to be the predominant type (60 to 100 per cent) found in blood serum. The ratio of phosphatidyl serine to phosphatidyl ethanolamine is variable.

The significance of these findings to the general problem of atherosclerosis will be presented.

3. An Evaluation of the Blood Lipids in Human Atherosclerosis: A Preliminary Report

J. C. Paterson, B. Cornish and E. C. Armstrong

Westminster Hospital, Department of Veterans' Affairs, and the Collip Medical Research Laboratory, University of Western Ontario, London, Ontario, Canada

An attempt is being made to evaluate, critically, the relationship between the levels of certain blood lipids, measured serially in living patients, and the actual amount of atherosclerosis found in these patients at autopsy. The serum cholesterol level, the cholesterol-phospholipid ratio and the S_f 12–20 lipoprotein concentration are being determined every six months in patients who are permanently confined to our hospital. Since this project was initiated 18 months ago, more than 20 patients in the series have died and have been examined at autopsy. The antemortem blood lipid levels have been compared with the autopsy findings in this group, and the impression has been gathered that, if the serum cholesterol level is below 300 mg. per 100 cc., minor variations in the serum cholesterol level, or elevations in the cholesterol-phospholipid ratio or the S_f 12–20 lipoprotein concentration, bear no relationship to the amount of atherosclerosis found at autopsy.

4. Serum Lipids in Carefully Selected "Atherosclerotic" and "Normal" Males

J. A. Little, H. M. Shanoff, R. W. Van der Flier and H. E. Rykert

Department of Veterans' Affairs, Sunnybrook Hospital, Toronto, Ontario, Canada

Seventy-seven male veterans from the Toronto area with proven coronary atherosclerosis were studied with reference to serum cholesterol, serum phospholipid, and lipoprotein fractions as determined by the ultracentrifuge method. Patients were selected only if their course was uncomplicated by hypertension, by diseases commonly associated with hypercholesterolemia (diabetes mellitus, hypothyroidism, familial hypercholesterolemia or the nephrotic syndrome), or by debilitating diseases. These patients are being followed over a 10-year period in an attempt to determine any relationship between the serum

lipid factors and the course of their disease. This paper is a preliminary report of the first two years of the study.

A control group with approximately 25 male veterans in each decade was also studied. They were all normotensive; all had normal electrocardiograms and none had any disease commonly associated with hypercholesterolemia. Comparison between the control group and the group with coronary atherosclerosis was confined to the sixth and seventh decades in which there were a significant number of patients. The two groups were compared with regard to serum lipid values, body build, obesity, abdominal aortic calcification, physical activity and other relevant clinical data. In the control group the mean total serum cholesterol (Schoenheimer-Sperry) and the standard deviation for each decade beginning with the fourth were: 204 ± 29, 215 ± 37, 206 ± 3, 215 ± 40 and 212 ± 40 mg. per 100 cc. In this group the total serum cholesterol did not seem to vary with age. The mean total serum cholesterol and the standard deviation for the sixth and seventh decades of the coronary atherosclerosis group were 256 ± 47 and 229 ± 38 mg. per 100 cc., respectively. These were notably higher than the values obtained for the control group. The ratio of free to total serum cholesterol was the same in both groups. The serum phospholipid (Zilversmit and Davis) maintains the same relationship to total serum cholesterol in both groups; that is the C/P ratio for any defined range of total serum cholesterol was similar in both groups. The serum lipoproten patterns for both groups were compared.

5. A Serum Lipoprotein Pattern Characteristic of Biliary Obstruction, with Some Comments on "Jaundice Due to Methyltestosterone"

Robert H. Furman, Loyal L. Conrad and R. Palmer Howard

Oklahoma Medical Research Foundation and Department of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Utilizing ultracentrifugation with a solvent density of 1.063, McGinley and colleagues dedetermined that "practically no lipoproteins" of a flotation rate greater than S_f 17 are found in subjects with biliary obstruction.

We have employed a solvent density of 1.21, after the modification of Lewis, which permits estimation of "alpha-$_1$" and "alpha-$_2$", as well as "beta" and less dense lipoproteins.

In 25 subjects with biliary obstruction due to a variety of causes, consistently reduced alpha-$_1$ levels were noted; often virtually no alpha-$_1$ peak could be discerned. Alpha-$_2$ and beta lipoproteins appeared to undergo simultaneous flotation. Following relief of obstruction there was a marked increase in alpha-$_1$ concentration and a concomitant reduction in the amount of S_f 10–20 (−S 40–70) lipoprotein.

Biliary obstruction therefore is associated with characteristic alteration of "high" as well as "low" density lipoproteins.

Studies in 12 subjects indicate that methyltestosterone administration produces a similar reduction in alpha-$_1$ concentration. One subject receiving 200 mg. daily of methyltestosterone became jaundiced at a time when his ultracentrifuge patterns indicated almost complete absence of lipoproteins of alpha-$_1$ flotation rate characteristic. Cholecystograms were normal; routine tests were compatible with biliary obstruction.

It is suggested that methyltestosterone influences hepatic function with biliary obstruction as a possible consequence.

6. First Interim Report on the Effects of Estrogen Therapy in Males under 50 Years of Age with a Previous Single Myocardial Infarction

Jeremiah Stamler, Ruth Pick and Louis N. Katz

In collaboration with Doctors S. Cogan, B. W. Carnow, H. Gold, B. M. Kaplan, W. R. O'Connor, E. Kaplan, L. Baker and Miss D. Friedman

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Department of Medicine, Chicago, and Veterans Administration Hospital, Hines, Ill.

Based on experimental findings in this laboratory demonstrating that estrogens are effective against cholesterol-induced coronary atherosclerosis in chicks, a long-range study is in progress on the possible efficacy of estrogens in the treatment of human coronary atherosclerosis. During the last two years, 100 patients have been brought under observation. Of these, 69 are males under 50 years of age who have recently had a single proved myocardial infarct and therefore meet the criteria for this study. They were divided into two groups on a "double blind" basis—estrogen-treated and placebo. Analysis of these groups as of June 30, 1954, revealed them to be practically identical: mean age, 40.6 and 40.0 years; mean initial weight, 168.5 and 161.3 pounds; mean duration after infarct when study was begun 5.4 and 3.6 months; mean duration of treatment, 8.3 and 6.6 months (maximum: 19 and 18 months); mean pretreatment plasma cholesterol level, 237 mg. per 100 cc. and 261 mg. per 100 cc.; mean pretreatment plasma total cholesterol-lipid phosphorus (C/P) ratio, 21.8 and 23.4 mg. per 100 cc. Oral estrogen dosages were increased stepwise from an initial level from 1.25 or 2.5 mg. of mixed conjugated equine estrogens (Premarin) to 4.0–10.0 mg. Estrogens tended to induce gynecomastia, loss of libido and impotence—side effects which only rarely resulted in discontinuation of therapy. The 1.25 to 4.0 mg. dosages had no effect on plasma total cholesterol levels. Higher dosages tended moderately to lower the plasma C/P ratio.

As of June 30, 1954, in the placebo group of 26 patients under treatment for two months or longer, a second proved myocardial infarction had occurred in six, with three fatalities. In contrast, in the group of 39 under estrogen treatment for two months or longer, no recurrence of myocardial infarction had occurred. Neither the size of groups nor the duration of treatment justifies any definitive conclusions concerning the significance of these initial observations. However, continuation and expansion of this investigation would seem highly warranted.

7. Effects of Long-Term Estrogen and Heparin Administration on Serum Lipoprotein Levels in Hypercholesterolemic Humans

Edwin Boyle

Laboratory of Metabolism, National Heart Institute, Department of Health, Education and Welfare, National Institutes of Health, Bethesda, Md.

A group of hypercholesterolemic patients with xanthomatosis tuberosum and/or tendinosum, or with proven coronary artery disease was observed for periods up to two years. During this period, varying doses of ethinyl estradiol or subcutaneous 20 per cent solution of sodium heparin were administered. Serum samples were analyzed for total cholesterol, free cholesterol, phospholipid, and neutral fat at frequent intervals. Serum lipoproteins were determined by analytic ultracentrifugation at a density of 1.21 for alpha$_1$ and low-density beta components.

The resulting alterations in serum lipids and

lipoproteins were marked with both agents. Heparin administration was accompanied by reduction of the low-density beta components and varying changes in the alpha$_1$ components. There was reduction in all serum lipids with a decrease in the cholesterol-phospholipid ratio. Ethinyl estradiol administration was accompanied by a marked decrease in all beta components, increase in alpha components, and also reduction in all serum lipids with a decrease in cholesterol-phospholipid ratio.

8. An Evaluation of the Effect of Choline and Inositol on the Clinical Course and Serum Lipids in Patients with Angina Pectoris

Raymond S. Jackson, Chas. F. Wilkinson, Jr., Lawrence Meyers, Michael S. Bruno, and Martin R. Benjamin

New York University–Bellevue Medical Center New York Post-graduate Medical School, New York, N. Y.

Forty patients with agina pectoris were studied in a double-blind experiment testing the effect of a choline-inositol syrup on their symptoms and on their plasma lipids. A randomized series was followed in starting these subjects on either the choline-inositol syrup or placebo. After six months on the first preparation, they were given a three-week supply of a mixture of the two in order to minimize the slight taste difference. Then they were given the second preparation for six more months.

Each day, these subjects recorded upon a report card the relative amount of pain experienced and the number of nitroglycerine tablets taken. At three-week intervals, they were weighed, and blood was secured for determinations of plasma cholesterol and phospholipid.

The data were subjected to independent statistical analysis. Choline-inositol therapy produced no significant effect upon the symptoms and the nitroglycerine intake of these subjects. The mean plasma cholesterol and phospholipid levels were significantly higher while on choline and inositol, but the mean phospholipid–free cholesterol ratio was not significantly altered. Fluctuations of total cholesterol and of phospholipid were not affected by choline-inositol therapy.

9. The Production of Cardiovascular Damage in Young Rats by a Dietary Deficiency of Lipotropic Factors

W. Stanley Hartroft

Banting and Best Department of Medical Research, University of Toronto, Toronto, Ontario, Canada

Fifty to eighty per cent of young male rats of the Wistar strain (85 to 100 Gm.) fed a low choline diet for periods of three to five weeks, develop cardiac muscle necrosis, abnormal fat deposits in coronary arteries and aortic sclerosis (grossly visible in about 15 per cent). Lesions are associated with a high incidence of acute and subacute necrosis of tubules in cortices of both kidneys; all animals exhibit large amounts of abnormal fat in their livers. Choline (0.85 per cent) added to the basal diet, (offered to and consumed in the same amounts by control animals of comparable age, sex and weight) completely prevents all abnormalities in heart, vessels, kidneys and liver. A number of additional factors that were suspected to play accessory roles in aiding development of the lesions have been investigated, including the animals' caloric intakes, vitamin E supplements, excessive amounts of vitamin D, level of dietary fat, etc. The results of these studies and their significance will be discussed. The pathogenesis

of the cardiac and vascular lesions will be presented with the aid of color-transparencies. The vascular lesions may be (1) the direct result of dietary choline deficiency, or (2) secondary to induced renal damage of dietary origin, or (3) they may be manifested by a combination of both (1 and 2). Evidence supporting these various theories of the etiology of cardiovascular damage of nutritional origin will be discussed briefly.

10. Absorbability of Dihydrocholesterol and Sitosterol

R. Gordon Gould

With the technical assistance of K. C. Kohr and L. Virginia Lotz

Los Alamos Scientific Laboratory, University of California, Los Alamos, N. M.

Early studies of Schoenheimer, Page and others failed to show detectable absorption of dihydrocholesterol or sitosterols by chemical identification methods. Since large amounts of these sterols are at present being fed to patients it is of interest to re-examine the question of their absorbability by means of the more sensitive method of feeding radioisotope-labeled sterols. C^{14} and tritium-labeled dihydrocholesterol have been fed to rats and the absorption determined by the amount of isotope in tissue sterol fractions in comparison with labeled cholesterol. Dihydrocholesterol was absorbed, although to a considerably smaller extent than cholesterol. Purification through the crystalline dibromide showed the isotope to be present in cholesterol, proving the conversion of dihydrocholesterol into cholesterol.

Mixed sitosterols and pure beta-sitosterol were labeled with tritium by exchange and fed to rats and humans. Preliminary results in humans indicated the total amount of T-sterols in blood and liver was about 0.1 to 1.0 per cent of the 400 mg. dose fed. The rate of disappearance from blood was much faster than for labeled cholesterol suggesting the possibility that sitosterol does not accumulate in the body partly because of rapid excretion. Rat experiments showed that T-beta-sitosterol was absorbed although not as efficiently as T-cholesterol. Absorption of these sterols cannot be considered a contraindication to their therapeutic use, because there is no evidence that the total sterol content of any tissue increases no matter how much is fed.

11. The Serum Cholesterol Level and Lipoprotein Pattern Following the Administration of Plant Sterols

Claude R. Joyner and Peter T. Kuo

Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pensylvania, Philadelphia, Pa.

The double-blind method was employed to study the effect of plant sterol ingestion upon the serum cholesterol level and lipoprotein pattern in normocholesteremic and hypercholesteremic patients consuming an unrestricted diet. A control period of four to six weeks was established at the beginning and end of the study. The administration of a sitosterol suspension before meals in a dosage of 12 to 24 Gm. per day resulted in a significant decrease in the serum cholesterol level in all patients. The degree of the decrease of the blood cholesterol level was correlated with the dosage, and no effect was found with a dosage less than 10 Gm. per day. The greatest decrease in cholesterol was obtained in patients having the highest control cholesterol values.

The serum lipoprotein pattern obtained by paper electrophoresis revealed a relative lowering of the beta lipoprotein peak following sterol administration. None of the patients objected to the medication employed in this study, and no untoward side reactions were observed.

12. Effects of Prolonged Administration of Sitosterol on Serum Lipids

Maurice M. Best, Charles H. Duncan, Joan D. Wathen, Edward J. VanLoon and Robert E. Shipley

University of Louisville School of Medicine, Veterans Administration Hospital, Louisville, Ky., and Lilly Laboratories for Clinical Research, Indianapolis, Ind.

The ingestion of sitosterol has been shown to result in a lowering of serum cholesterol. To further explore the effects on the various serum lipid fractions of prolonged administration of this plant sterol the following studies have been conducted. Fifteen to 18 Gm. per day of beta-sitosterol was administered orally in divided doses, immediately before the ingestion of food, for periods up to one year to 16 patients, the majority of whom were hypercholesterolemic. There was no restriction as to type or amount of diet. Frequent determinations were made during control and treatment periods of serum total cholesterol, lipid phosphorus, and total lipid; from these values neutral fat was calculated. Ultracentrifuge analysis of lipoproteins was performed on selected sera.

A significant reduction was observed not only in serum cholesterol but also in total lipid and calculated neutral fat. The mean fall in serum cholesterol was 16.4 per cent, in total lipid 13.9 per cent, and neutral fat 18.4 per cent. In the limited number of sera analyzed a fall in S_f 5–9, 10–30, and 30–100 classes of lipoproteins occured. These studies confirm the hypocholesterolemic effect of beta-sitosterol, and indicate that its ingestion also results in a lowering of serum neutral fat and total lipid.

13. Studies of Normal Endogenous Lipemia Clearing Factor

Hyman Engelberg

Cedars of Lebanon Hospital, Los Angeles, Calif.

Previous studies by several groups have failed to demonstrate the existence of lipemia clearing factor unless heparin is injected or shock is produced in animals. This failure to demonstrate endogenous clearing factor as normally present in blood, and the lack of unequivocal proof that heparin itself is a normal constituent of the circulating blood, are the major barriers to the acceptance of the role of heparin in the physiologic transformation of serum lipoproteins. Since the presence of heparin in plasma has recently been demonstrated (Am. J. Clin. Path., May 1954), and since heparin levels varied inversely with serum lipoproteins, it seemed logical that endogenous lipemia clearing factor might be found in those individuals in whom serum lipids and lipoproteins are usually low.

Clearing factor was occasionally found in varying amounts in adolescents, in young women, and in several older men and women who had very low serum lipids. The fat substrate used to demonstrate clearing was a Tween stabilized emulsion of sesame oil. In several individuals endogenous clearing factor had one-third the activity of that produced by the injection of 25 mg. of heparin. The results of plasma heparin and serum lipase determinations will also be presented in these patients.

14. Effects of Heparin on the Development of Atherosclerosis and of Fatty Liver in Cholesterol-Fed Rabbits

H. C. Meng and William S. Davis

Department of Physiology, Vanderbilt University School of Medicine, Nashville, Tenn.

The present investigation was undertaken to study: (1) the effects of daily intravenous administration of small doses of heparin on the development of atherosclerosis and of the

accumulation of fat in the liver in cholesterol-fed rabbits; (2) the relationship between the incidence of atherosclerosis and the ability of postheparin plasma of these animals to clear the turbidity of neutral fat emulsion in vitro. This abstract constitutes our preliminary findings.

It was found that daily intravenous injection of 1.0 to 2.5 mg. heparin per kilogram failed to suppress the development of atherosclerosis significantly in cholesterol-fed rabbits. Atherosclerotic lesions were observed, grossly and/or microscopically, in 93 per cent of the rabbits receiving no heparin treatment, while in heparin treated animals 78 per cent showed such pathologic changes. However, marked amelioration of fatty liver was demonstrated in the heparin treated group. Only 22 per cent of the heparin-treated animals showed fat accumulation in the liver compared with 73 per cent of the nontreated group.

A reversed relationhsip between the clearing of neutral fat emulsion by the postheparin plasma and the incidence of atherosclerosis in both groups of animals seemed to exist. In rabbits whose postheparin plasma showed high activity of clearing, either no atherosclerotic lesion was demonstrated or it was very mild even microscopically. Conversely, in rabbits whose postheparin plasma showed low clearing activity, marked atherosclerotic lesions were usually observed. The average serum total cholesterol was increasingly higher in the heparin-treated group than that of the nontreated animals. There was no significant difference in the body weight between the two groups. The significance of the results will be discussed.

15. Heparin-Like Activity of Polymetaphosphate

Richard J. Havel and Joseph H. Bragdon

Laboratory of Metabolism, National Heart Institute, National Institutes of Health, Bethesda, Md.

Lipemia clearing factor, a lipolytic enzyme appearing in plasma following heparin administration, catalyzes the lipolysis of chylomicrons and low-density lipoproteins. It has recently been shown in this laboratory that certain inorganic salts are also capable of eliciting the appearance of clearing factor in plasma as well as interfering with blood coagulation. In rats, intravenously administered sodium polymetaphosphate of high molecular weight, produced by fusion of sodium dihydrogen phosphate, is as effective as heparin in eliciting the appearance of clearing factor (minimal effective dose: 0.05 mg. per kilogram). Its anticoagulant activity, however, is considerably less than that of heparin. Heparin cofactor appears to be essential for the anticoagulant activity. Both the anticoagulant and clearing factor activities are inhibited by protamine. These observations support the concept that these effects of heparin are nonspecific, since they are also produced by other negatively charged polyelectrolytes.

16. Studies on Clearing Factor, a Lipoprotein Lipase

Edward D. Korn

Laboratory of Metabolism, National Heart Institute, National Institutes of Health, Bethesda, Md.

A soluble enzyme preparation from normal rat heart which has all the properties of clearing factor obtained from the plasma of heparin-injected animals has been described elsewhere. This enzyme catalyzes the lipolysis of chylomicrons and low-density, soluble lipoproteins but not of coconut oil. Coconut oil is hydrolyzed only after preincubation with normal serum. The enzymatic activity is stimulated by heparin and inhibited by protamine. It is also inhibited by 1 M salt. This inhibition is not reversible by dialysis or the addition of heparin or a boiled extract of an active enzyme preparation to the dialyzed protein. Inorganic

pyrophosphate, adenosine triphosphate, inosine triphosphate, uridine triphosphate and adenylic acid all inhibit at levels of 0.005 to 0.01 M. This inhibition is reversed by heparin. Polymetaphosphate, which induces clearing factor production in vivo, will substitute partially for heparin. These data indicate that clearing factor is a lipoprotein lipase in contrast to other lipases which hydrolyze free triglycerides more rapidly than lipoproteins. Heparin appears to be the normal co-factor which can be competitively replaced by functionally inactive anions.

17. Production of Atherosclerosis in the Rat, an Omnivorous Mammal, by Forced Feeding of Vegetable Oil: Preliminary Report

Manuel R. Malinow, David Hojman and Amanda A. Pellegrino

Pabellon de Cardiologia Inchauspe, Hospital Ramos Mejia, Buenos Aires, Argentina

The histology of the aorta was studied in four groups of rats. These were (a) control animals, (b) animals with unilateral cellophane perinephritis (c) normal animals force-fed with vegetable oil and (d) animals with unilateral cellophane perinephritis subjected to force-feeding with vegetable oil.

No lesions were found in control group (a). Rats of groups (b) and (c) showed occasional lesions consisting of cholesterol infiltrates in the endothelium and subendothelium. In rats of group (d) the arterial lesions were more severe and included endothelial and subendothelial proliferation, lipid infiltration and formation of plaques with necrosis thereof.

The fat-fed animals showed moderate elevations of blood cholesterol.

The fact that lesions were found in animals in which exogenous cholesterol supply was low, indicates the importance of fat, rather than cholesterol metabolism as such, as a factor in atherogenesis, and the production of lesions in animals with an experimental renal lesion calculated to elicit hypertension suggests that hypertension contributes to atherogenesis in such species.

18. Production of Hyperlipemia and Lipoid Infiltration of Intima and Media of Aorta by a High Fat, Cholesterol-Free Diet

Alfred Steiner and Seymour Dayton

Columbia University Research Service, Goldwater Memorial Hospital, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Recent clinical observations here suggested that dietary fat of vegetable origin might be as significant as the ingestion of cholesterol in the maintenance of the serum cholesterol levels of man. Experimental atherosclerosis, however, has not been produced in any species without the feeding of cholesterol. The feeding of high fat diets of vegetable origin have failed to result in arterial lesions. Because of the possible relationship of diet to atherosclerosis, further study of this problem is indicated. For this reason a preliminary experiment has been carried out in which rabbits were placed on a diet containing 28 per cent vegetable fat, but free of cholesterol, and the effects upon serum lipids and arteries were determined. A moderate increase in the total serum lipids, serum cholesterol, and serum phospholipids resulted. At the end of 12 months, three of the four rabbits on the high fat diet were found to have

poid infiltration of the intima and underlying media of the aorta. Similar lesions were not present in control animals. Additional studies in a second group of rabbits are in progress.

19. The Effects of Certain Vegetable and Animal Fats on Plasma Lipids of Humans

J. M. R. Beveridge, W. Ford Connell, G. Mayer, J. B. Firstbrook and Margaret DeWolfe

Departments of Biochemistry and Medicine, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada

Five apparently normal healthy male faculty members consumed homogenized diets of accurately known composition and amounts over a period of approximately four months. The diets varied in cholesterol content and provided variable proportions of the caloric intake in the form of fat and carbohydrate. The nature of the fat was also altered, both vegetable and animal fats being utilized. The type of protein and the proportion of protein calories was kept constant throughout. The results demonstrated unequivocally that there is a profound difference between the two types of fat tested. An increase from 28 per cent to 58 per cent of the total calories in the form of vegetable fat did not lead to an increase in plasma lipid levels, whereas when the same amount of animal fat was supplied a significant increase occurred. The addition of the same amount of cholesterol present in the animal fat to the vegetable fat did not alter the picture. It is concluded that there is a factor or factors present in the animal fat tested and absent from the vegetable fat that, per se or in conjunction with some other dietary component, causes an elevation in plasma lipid levels.

20. Further Experience with High Vegetable-Fat Diet in Patients with Extensive Diabetic Vascular Disease

Laurance W. Kinsell, Gilbert C. Cochrane, Sadie Smyrl, George Fukayama and Majorie Coelho

Institute for Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

As previously reported, the administration of diets containing large amounts of vegetable fat with little or no animal fat to all individuals studied (that is, those with normal, elevated, or low serum cholesterols) results in a striking decrease in the serum cholesterol level. The possible interpretation and clinical significance of this observation has been under constant investigation during the past three years. On the basis of these studies, the following statements appear in order:

1. No derivative of vegetable fat (sterol or phospholipid) so far evaluated will produce the results having the consistency or the magnitude of those produced by the use of vegetable fat, per se.

2. Mixed diets containing large amounts of vegetable fat have been devised for long-term administration to patients with extensive atherosclerosis, with or without marked hypercholesterolemia. Cautious interpretation of the clinical observations in these patients suggests that such diets may have a desirable effect upon the vascular disease.

21. The Biosynthesis of Cholesterol and Its Accumulation by the Whole Aorta Maintained in Vitro

Nicholas T. Werthessen

Department of Physiology and Biochemistry, Southwest Foundation for Research and Education San Antonio, Tex.

A technic for the prolonged maintenance of the calf aorta in vitro has been developed. Aortas have apparently survived and maintained their capacity to biosynthesize cholesterol from acetate in these systems for periods as long as 300 hours. Investigations of the biochemistry of the situation have shown that under hypertensive conditions the aorta accumulates more cholesterol than under normotensive or hypotensive conditions. Accumulation of cholesterol is associated with an increment of lipoproteins in the perfusate. Loss of cholesterol from the aorta is accompanied by loss or maintenance of the original lipoprotein titre of the perfusate. The lipoprotein data in association with studies of isotope accumulation in the perfusate indicate the possibility that the cholesterol accumulation seen in these experiments is due to newly synthesized cholesterol and that such cholesterol can be released from the aorta into the perfusate.

Preliminary histopathologic studies indicate that the in vitro situation studied in those experiments may be a useful tool in the attack on the general problem of atherosclerosis.

22. Aortic Synthesis of Phospholipids in Experimental Rabbit Atheromatosis

Moris L. Shore, D. B. Zilversmit and R. F. Ackerman

Divisions of Physiology, Preventive Medicine and Medicine, University of Tennessee, Memphis, Tenn.

We have previously suggested that the accumulation of phospholipids by the aorta of atherosclerotic rabbits results from increased synthesis in situ rather than deposition of plasma phospholipid (Zilversmit and colleagues: Circulation **9:** 581, 1954). Further evidence for this hypothesis is presented. Normal rabbits and rabbits maintained on a high cholesterol diet for five months were injected with $P^{32}O_4$ or with labeled plasma phospholipid. Caclulations based on the activity of aortic phospholipid and the average specific activity of plasma phospholipids in these experiments indicate that deposition of plasma phospholipids can account for only a small fraction of the radioactivity found in aortic phospholipid when labeled phosphate is administered. This suggests that the labeled phospholipid in the aorta is primarily synthesized by that organ. A comparison of the specific activities of aortic phospholipid with plasma lecithin, sphingomyelin, and cephalin six hours after $P^{32}O_4$, suggests that none of these plasma phospholipid fractions satisfies the requirements for precursor of aortic phospholipid. This agrees with our previous conclusion that increased arterial synthesis is responsible for the accumulation of aortic phospholipids in cholesterol-fed rabbits.

23. Rates of Acetate Turnover and Lipid Synthesis in Normal, Hypothyroid, and Hyperthyroid Rats

Seymour Dayton, Joan Dayton, Fred Drimmer and Forrest E. Kendall

Research Service, First Division, Goldwater Memorial Hospital, and Departments of Medicine and Biochemistry, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Methods have been devised for estimating in individual rats the rates of several pathways concerned with acetate metabolism. Sodium acetate-1-C^{14} was administered by constant intravenous infusion to anesthetized animals fed aminophenylbutyric acid. Radioactivity measurements were made of respiratory carbon dioxide, tissue cholesterol, fatty acids, and of the excreted acetylamino acid. It was possible to calculate, from these data, the rate of turnover of acetate, the rates of synthesis of cholesterol and fatty acids from acetate, and the percentage of respiratory carbon dioxide derived from acetate. Information on these metabolic functions has been obtained in normal, hypothyroid and hyperthyroid rats.

The rates of acetate turnover and of synthesis of cholesterol and fatty acids from acetate were all found to be directly proportional to the basal metabolic rates of the animals, with a high degree of correlation. Changes in the metabolic rate apparently affected the different pathways of acetate metabolism in the same manner and degree.

Significant alterations in tissue lipid concentrations were also observed. The most striking of these was a rise in liver cholesterol and fatty acid concentrations in the hyperthyroid animals.

24. Uptake of Radioactive Sulfur by Vascular Tissue

Robert C. Buck

Department of Microscopic Anatomy, University of Western Ontario Medical School, London, Ontario, Canada

Normal rabbits and dogs and cholesterol-fed rabbits were injected intravenously or intramuscularly with radioactive sulfur (S^{35}) as sodium sulfate (0.6 to 1.0 mc. per kilogram). At intervals of 24 or 48 hours after injection the uptake of radioactive material was studied in the aorta and pulmonary artery and in muscular walled arteries of various sites. Autoradiography was the principal method used to assess the S^{35} incorporation.

Normal aorta was found to have the greatest isotope concentration in the upper thoracic region and less in the abdominal part. Muscular arteries, such as the femoral or splenic showed only a comparatively slight S^{35} uptake while the branches of the pulmonary artery had an intermediate concentration.

In the aorta and pulmonary artery the isotope was distributed throughout the media, but the concentration was highest towards the intimal surface. The adventitia contained relatively little S^{35}. The isotope incorporated into muscular-type arteries tended to be diffusely distributed through the wall but was sometimes concentrated near the intima.

Intimal lesions of the aorta of cholesterol-fed rabbits incorporated S^{35} in much higher concentrations than any part of the wall of the normal aorta. On the other hand the media underlying the intimal lesions in cholesterol-fed rabbits showed a much lower isotope concentration than that of the media in normal rabbits.

25. Immunochemical Relationship of the Protein Moieties of Human Plasma Beta Lipoprotein and Chylomicrons

Elliott Middleton, Jr.

Laboratory of Metabolism, National Heart Institute, Bethesda, Md.

Immunochemical methods have been used to study the relationship between the protein component of S_f 3–8, beta-lipoprotein and the protein associated with chylomicrons.

Rabbit antiserum was prepared against ultracentrifugally isolated alum-precipitated human plasma beta-lipoproteins (S_f 3–8). This antigen was homogeneous by ultracentrifugal analysis. The antiserum, however, contained at least three different antilipoprotein antibodies as determined by quantitative precipitin and Oudin agar diffusion tests. Human plasma chylomicrons were prepared by ultracentrifugal flotation at 9500g and were washed one or two times by centrifugation through 0.15 M sodium chloride. Such preparation gives a product which is less than 1 per cent protein.

Fresh chylomicron suspensions did not react with the anti-beta-lipoprotein rabbit serum. After hydrolysis with a dilute steapsin extract, however, precipitate formation occurred. After partial absorption of the anti-beta-lipoprotein serum with a beta-lipoprotein preparation, the antiserum still gave some precipitate with steapsin-treated chylomicrons. No reaction was obtained between hydrolyzed chylomicrons and a rabbit antiserum to purified human serum albumin.

These preliminary data suggest that the protein or proteins associated with chylomicrons are very similar to those of beta-lipoprotein.

26. Blood Chemical Studies in Depancreatized Rabbits on Various Diets

O. J. Pollak, W. George Chubaty, Irene R. Mazer and Joyce S. Evans

Kent General Hospital, Dover, Del.

Series of rabbits on a standard diet were subjected to 16 different experiments: Cholesterol, cottonseed soil, and cholesterol in oil, minus/plus pancreatin were fed to intact animals and to depancreatized animals for two weeks. Weekly, blood was assayed for total protein, lipids and cholesterol, and proteins, lipoproteins, and glucoproteins were partitioned by paper electrophoresis.

Serial and individual normal fluctuations of blood chemical constituents were ascertained. Daily feeding of 10 ml. cottonseed oil caused moderate transitory lipemia. Daily feeding of 2 Gm. of cholesterol in capsules resulted in an increase in total protein, decrease of albumin, increase of beta and gamma globulin, increase in total lipid, cholesterol, and total lipoprotein, depression of alpha and rise of beta lipoglobulin. Feeding of 2 Gm. cholesterol in 10 ml. oil resulted in blood chemical alterations similar to those observed after ingestion of cholesterol alone, but aggravated; return to normal values was much delayed. Daily addition to the diet of 1 Gm. of pancreatin in capsules failed to influence blood in either series. Glucoproteins remained within normal limits in all experiments.

Removal of from four-fifths to five-sixths of the pancreas caused only slight and erratic aggravation of blood changes in all series. Daily supplementary feeding of 1 Gm. of pancreatin, from the day of surgical operation on, had a dramatic effect: The maximum degree of the various blood chemical changes was roughly one-half of that in the corresponding series of rabbits not fed pancreatin, and, consequently, the values reverted to normal levels in half the time it took in the corresponding series.

27. The Rate of Regression of Hypercholesteremia and Atherosclerosis in Chicks: Effects of Diet, Pancreatectomy, Estrogens and Thyroid

Simon Rodbard, Ruth Pick and Louis N. Katz

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

With the cessation of cholesterol feeding in young chicks, plasma cholesterol falls to normal within a week. Coronary atherosclerosis regresses more slowly, while aortic atherosclerosis is relatively persistent. These rates of regression can be affected by alimentary as well as endocrine factors in the regression phase. The regression rate was retarded by inanition produced by limited caloric intake, or by feeding of indigestibles. Regression was also retarded by very small amounts of cholesterol (0.1 per cent) in the diet during the unloading period. This contrasts with the minimal effects of such small amounts in the diet in inducing hypercholesteremia and atherosclerosis. Addition of 5 per cent cottonseed oil or of oleomargarine to the regular diet did not affect the rate of regression.

Regression was markedly delayed in pancreatectomized chicks returned to a regular diet. Estrogens administered during a regression period maintained the hypercholesteremia and produced hyperphospholipemia, but the coronary lesions regressed at the same rate as in animals returned to a regular diet without estrogens. This suggests that estrogens do not affect the ability of the coronary vessels to dispose of infiltrated lipids; instead it may signify that circulating cholesterol in estrogen-treated chicks is of a type which does not freely enter the vessel wall. Addition of thyroid extract to the diet increased the rates of fall of plasma cholesterol and of the regression of coronary atherosclerosis.

28. Transient Hyperlipemia and Atherogenesis in Rabbits Following the Intravenous Injection of Colloidal Solutions

Elizabeth V. Lautsch, Gardner C. McMillan and G. Lyman Duff

Department of Pathology, Pathological Institute, McGill University, Montreal, Quebec, Canada

Nine rabbits between three and four months old were maintained on a diet free of cholesterol. They were injected intravenously with a single dose of 3 cc. of colloidal thorium dioxide (Thorotrast) per kilogram of body weight. Daily determinations of the free and total cholesterol, lipid phosphorus and fatty acid content of the serum were made. It was observed in all cases that the serum total cholesterol was increased from two to four times the normal values 24 hours following the injection. The serum free cholesterol, lipid phosphorus and fatty acid content were also increased. Normal values were gradually re-established during the ensuing five days.

An additional eight rabbits maintained on a cholesterol-free diet were injected intravenously with from 20 to 40 cc. of a 0.5 per cent to 1.2 per cent w/v aqueous solution of methyl cellulose (1500 cps.). Three of the rabbits manifested an increased lipemia following the injection like the rabbits injected with Thorotrast. One rabbit had a content of 468 mg. of cholesterol per 100 cc. in its serum 24 hours after injection.

No disturbance was observed in the serum lipids of five rabbits injected intravenously with 50 cc. of physiologic saline.

Microscopic examination from their endothelial surface of the aortas of those rabbits that had experienced an appreciable elevation in their serum lipids disclosed the presence of small focal accumulations of lipid contained within macrophages in the intima. The lipid accumulations were attributed to the disposition of lipid material of endogenous origin.

29. Tissue Permeability: A Factor in Experimental Atherosclerosis. Studies with Cortisone and Hyaluronidase

Chun-I Wang, Louis E. Schaefer and David Adlersberg

Mount Sinai Hospital, New York, N. Y.

Administration of cortisone or hydrocortisone to cholesterol-fed rabbits resulted in marked additional elevation of all lipid fractions provided that no toxic doses of the hormones were used. Plasma cholesterol levels up to 5000 mg. per 100 ml. were observed (J. Clin. Investigation **32:** 550, 1953). Despite extremely high lipid levels, these animals show marked inhibition of atherogenesis and delayed development of skin and joint xanthomata. Diminished tissue permeability offers an explanation.

Twenty-seven rabbits were fed 1 Gm. of cholesterol per day for four weeks; plasma cholesterol rose to 910, esterified cholesterol to 606 and phospholipids to 442 mg. per 100 ml. The animals were then divided into three groups: group A received cholesterol chow only; group B cholesterol chow and cortisone (1.5 mg. per kilogram per day); group C cholesterol chow, cortisone (1.5 mg. per kilogram per day) and hyaluronidase (1,000 TRU/day).

Groups	No. of Animals	2 Weeks		4 Weeks	
		Cholesterol Tot/Est mg./100 ml.	Phospholipids mg./100 ml.	Cholesterol Tot/Est mg./100 ml.	Phospholipids mg./100 ml.
Group A	5	1142/828	455	1380/1055	486
Group B	11	2576/1752	972	3540/2592	1316
Group C	11	1805/1325	743	2332/1697	928

Administration of cortisone (group B) enhanced the elevation of plasma cholesterol and phospholipid in the cholesterol fed rabbit after two and four weeks. Addition of hyaluronidase (group C) counteracted the cortisone effect and resulted in lower plasma lipid levels than in group B. Seifter noted an antihypercholesteremic and atherosclerosis-promoting effect of hyaluronidase and explained this effect by increased tissue permeability. In contrast, administration of cortisone promotes hypercholesteremia but retards deposition of cholesterol in aorta, skin and joints perhaps by decreased tissue permeability. These observations shed light on the important role of the ground substance in atherosclerosis.

30. Morphogenesis of Atherosclerosis in Swine Aortas

Howard L. Gottlieb

Bjorksten Research Foundation, Madison, Wis.

Recent examination of several thousand random swine aortas have revealed marked incidence of intimal lesions morphologically similar to minimal atherosclerotic lesions in humans.

Histologic studies of the lesions in swine have been made of serial sections of embedded and frozen specimens and by means of the endothelial surface staining technic.

The intimal structure of the swine aorta is very similar to the human aorta. A thin layer of connective tissues cells separates the endothelial lining from the media. As the chronologic age of the animal advances a gradual diffuse thickening of the subendothelial connective tissue layer was observable.

The gross lesions can be classified into two classic types: fibrotic and calcified. The fibrotic lesions can further be differentiated by the presence and absence of stainable lipid materials. A morphologic development of gross fibrotic lipid-containing lesions will be presented from the first discernible stages of appearance in the intima of lipid-like materials.

31. Observations on the Metabolism of Cholesterol-4-C^{14} in the Dog

Erwin H. Mosbach and Liese L. Abell

Columbia University Research Service, Goldwater Memorial Hospital, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Studies were carried out on cholesterol metabolism in dogs on low and high cholesterol diets using cholesterol-4-C^{14} as tracer. On the low cholesterol diet a 2.1 Kg. animal ingested *and* excreted approximately 40 mg. of cholesterol daily; on the high cholesterol diet the average daily cholesterol intake was 1.88 Gm., the average daily excretion 0.75 Gm. Following the oral administration of labeled cholesterol the radioactivity of serum sterols, fecal sterols, fecal acids and urine was determined daily. On the low cholesterol diet the dog had an average serum cholesterol level of 112 mg. per 100 ml.; on the high cholesterol diet this level was 287 mg. per 100 ml. In both experiments less than 3 per cent of the administered radioactivity could be detected in the serum sterols at any time; the high cholesterol diet did not appreciably affect the half-life of the serum sterols. After a period of 5 days 9.4 per cent of the administered radioactivity was recovered from the feces of the dog on the low cholesterol diet, while 63.5 per cent of the dose was recovered from the feces of the dog on the high cholesterol diet during a comparable period. The effect of thiouracil upon the metabolism of cholesterol-4-C^{14} will also be discussed.

32. In Vitro Production of Atheromata

William C. Felch, Louis B. Dotti and David J. Reisner

St. Luke's Hospital, New York, N. Y.

A reproducible experimental method for producing atheromatous lesions in vitro would permit control of tissue and serum variables while studying various factors in the pathogenesis of the disease. The following studies have investigated the possibility of such a method:

1. Studies of in vitro respiration in the Warburg apparatus at 37 C. of isolated rabbit aorta segments suspended in neutralized hyperlipemic rabbit serum revealed definite respiration for the duration of the experiments (nine hours), and equivocal respiration in segments which had previously been incubated in similar media for 24 hours and then placed in the Warburg apparatus.

2. No lesions were found when normal rabbit aorta segments were merely suspended in neutralized hyperlipemic rabbit serum at 4 C. or 37 C. for period of 6 to 72 hours.

3. No lesions were found when distally ligated aorta segments were suspended in Ringer's lactate with a constant distending pressure of intraluminal hyperlipemic serum.

4. When a continuous "jet" stream of hyperlipemic serum was directed at the exposed endothelial surface of normal aorta segments, lipid deposits were found which closely resembled minimal lesions of early in vivo atheromatosis. In some sections, however, the continuity of the endothelial surface was disrupted, and it was concluded that these deposits might represent artifacts produced by an unphysiologic experimental method.

5. Consequently, a pump-perfusion apparatus was constructed to simulate more closely in vivo conditions. Pulsating pressures of hyperlipemic serum in a continuous circulation were introduced for periods of 6 to 24 hours. The device was so constructed that total "systolic" pressure as well as the extraluminal pressure could be regulated.

With this apparatus, lipid deposits were demonstrated by Oil Red 0 staining of micro-

scopic sections, histologically indistinguishable from in vivo minimal lesions.

The effects of varying pressures, lipid concentrations, duration of incubation and other factors on the production of these lesions will be presented.

33. A Preliminary Report on the Prevention of Necrotizing Arteritis in Dogs by B Complex Vitamins and a Possible Interpretation

Jack C. Geer and Russell L. Holman

Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

Necrotizing arteritis has been produced with regularity in dogs by the feeding of a standard high fat diet for eight weeks or longer followed by the induction of standard renal insufficiency (usually with uranium nitrate).

The addition of certain B complex vitamins to the high fat diet during the last two weeks of preparatory feeding and the period of renal insufficiency has shown the lesions to be retarded or prevented by optimal amounts of thiamine, biotin, B_{12}, pantothenic acid and inositol but not by niacin, riboflavin, choline, or pyridoxine.

Consideration of the action of thiamine, biotin and pantothenic acid in the metabolic cycles has suggested the possibility of a biochemical basis for the arterial lesions. We are entertaining the hypothesis that under certain conditions the break-down products of fat metabolism are toxic or at least alter the ground substance and collagen at critical sites in the arterial system and that the products of glucose metabolism can remove these toxic substances either by carboxylation (biotin) or by supplying acetyl-Co A. This hypothesis has been strengthened by the finding that insulin and intravenous glucose also prevent or retard the arterial lesions.

34. Genetic Aspects of Idiopathic Hypercholesteremia: Studies of Parents and Offspring in Two Hundred Randomly Selected Families

David Adlersberg, Louis E. Schaefer, Arthur G. Steinberg and Chun-I Wang

Mount Sinai Hospital, New York, N. Y.

For the past two years we have been studying the prevalence of idiopathic hypercholesteremia in randomly selected 200 families in Staten Island, N. Y. This work represents a continuation of a previous study of 500 consecutive admissions to a large general hospital in New York City and of the families of the hypercholesteremic probands.

To date 119 families have been completed; in another 81 families determinations have been made in all but one or two available family members. The mean serum cholesterol levels of the *parents* arranged according to age approximate our previous data and those of other investigators. The mean serum cholesterol of the *children* remains essentially constant through age 12 (185 mg. per 100 ml.). A significant fall in serum cholesterol occurs in the age group 13 to 17 (172.1 mg. per 100 ml.; $p \cong 0.012$). This drop in cholesterol level at puberty may represent the effect of sexual maturation.

The ratio of esterified to total serum cholesterol remains unchanged in the hype-

cholesteremic parents and children (0.75 to 0.8). The phospholipid-cholesterol ratio is significantly lower in both hypercholesteremic parents and children in comparison with normocholesteremic parents and children (1.06 and 1.05 versus 1.21 and 1.27).

The parent-child interclass correlation coefficient for total serum cholesterol (based on 236 pairs in which the child was less than 13 years old) was found to be 0.315. The probability that this is a sample of a correlation coefficient equal to zero is approximately 0.000,001. The mid-parent-child interclass correlation coefficient was 0.485, $p \cong 0.000,000,1$. Finally the sib-sib intraclass correlation coefficient (based on 37 pairs, both members of which were less than 13 years old) was 0.458, $p \cong 0.004$.

Hypercholesteremia was significantly greater among children of hypercholesteremic parents than it was among children of normocholesteremic parents (13.5 versus 2.6 per cent; $p \cong 0.01$). In the previous study the prevalence of hypercholesteremia among children of hypercholesteremic parents was 35 per cent.

The major difference between the two samples is that, in the earlier sample, 93 per cent of the children were at least 18 years old while, in the present sample, 96 per cent are less than 18 years old. If, as has been previously postulated, the tendency to idiopathic hypercholesteremia is due to a dominant gene with incomplete penetrance, we must assume that penetrance increases with age. This is not an unprecedented assumption. The phenomenon is known to occur in such hereditary diseases as diabetes, psoriasis and multiple intestinal polyposis.

35. Approaches to a Therapy of Arteriosclerosis

Rudolf Altschul

University of Saskatchewan, Saskatoon, Saskatchewan, Canada

The following findings seem to point to a common mechanism for the inhibition of arteriosclerosis:

(1) Arteriosclerosis is due to tissue hypoxia or failure of respiratory enzymes (Hueper; Strughold; Rotter; Raska). (2) In the presence of air, ultraviolet irradiation causes oxidation of cholesterol (Hamano, 1925, and others). (3) After ultraviolet irradiation in the presence of air, cholesterol and egg yolk lose much of their atherogenic property in rabbits (Altschul, 1950). (4) Ultraviolet irradiation causes formation of peroxide in the living body (Lacassagne, and others). (5) Ultraviolet irradiation of rabbits receiving cholesterol orally, inhibits arteriosclerosis (Altschul, 1953). (6) Ultraviolet irradiation of patients with vascular diseases lowers in most cases the serum cholesterol after a single exposure (Altschul and Herman, 1953) and after repeated exposures Altschul, unpublished data). (7) Repeated subcutaneous injections of 250 to 300 cc. of oxygen lower the blood cholesterol in alcoholics (Smorodinzewa and Liwschitz, 1930). (8) Oxidized cholesterol (cholestenone, 7-ketocholesterol) does not produce arteriosclerosis in rabbits (Altschul, 1950). (9) Inhalation of oxygen at 60 to 65 per cent for one to three hours, three times weekly, inhibits arteriosclerosis in rabbits receiving cholesterol orally (Altschul, 1954). (10) Inhalation of oxygen at 40 to 45 per cent for two hours, in single or repeated doses, lowers serum cholesterol in a majority of patients with vascular diseases (Altschul and Herman, 1954).

It seems possible to lower serum cholesterol through oxidation in vivo by means of ultraviolet irradiation or oxygen inhalation. Since cholesterol is believed to be harmful to vulnerable vessels, or, if present in excess, also to normal vessels, the attempt to decrease it by oxidation appears warranted.

36. Lipoprotein Profiles in Normal and Pathologic States: Comparative Paper-Electrophoretic Studies in Man and Other Mammals

Elaine T. Bossak, Chun-I Wang and David Adlersberg

Mount Sinai Hospital, New York, N. Y.

Paper electrophoresis provides a simple technic for studying alterations in serum lipoproteins in pathologic states. Lipoprotein profiles were established in normal man and laboratory animals using Amidoschwarz 10B for protein-staining and Oil Red 0 for lipid-staining with quantitative estimations by densitometry. Species specificity of these profiles was demonstrated in man, monkey, dog and rabbit. Studies in progress include sera from 20 men and women with $alpha_1$ plus $alpha_2$ lipoproteins amounting to 35 per cent and beta lipoprotein (plus neutral fat) to 65 per cent of the total; in five male and female rhesus monkeys respective values were 41 per cent and 59 per cent; in six male dogs $alpha_1$ plus $alpha_2$ plasma lipoproteins totaled 69 per cent and beta lipoprotein 31 per cent; in four male rabbits values were 50 per cent for each fraction.

Serum lipid elevations in human nephrosis are characterized by marked increases in beta lipoprotein (plus neutral fat) to 94 per cent; $alpha_1$ plus $alpha_2$ averaged 6 per cent. In human myxedema corresponding values were 80 per cent and 20 per cent; after treatment an approximately normal profile of 70 per cent and 30 per cent was observed as serum lipid values became normal. Accompanying plasma lipid elevations in myxedematous dogs, alpha lipoprotein fell to 46 per cent, beta plus NF to 22 per cent, and a fraction with intermediate mobility appeared amounting to 32 per cent. In cholesterol-induced atherosclerosis in rabbits marked plasma lipid elevations were accompanied by NF (plus beta) fraction of 91 per cent with complete obliteration of the normal lipoprotein profile, resembling patterns obtained in humans with essential hyperlipemia. Serum lipid values fell in pyridoxine-deficient monkeys without alteration of the lipoprotein profile.

These changes in lipoprotein profiles are statistically significant and agree with results obtained by more elaborate technics.

37. The Production of Cardiac and Vascular Lesions by Feeding Deficient Diets

D. H. Copeland, W. D. Salmon and M. J. Burns

Department of Animal Husbandry and Nutrition, Alabama Polytechnic Institute, Auburn, Ala.

Numerous degenerative vascular and cardiac lesions have been observed in rats, chickens, and dogs fed for relatively long periods on diets low in choline and certain related factors.

The lesions observed in the heart consisted of endocardial, particularly valvular and connective tissue degeneration, with or without foci of myocardial degeneration. In the blood vessels, the degenerative changes were sometimes present in the intima, sometimes in the media, and sometimes in both. In the intima the lesions usually consisted of localized areas of swelling with edema and/or lipids. Some intimal lesions were simply spicules of calcium with no histologic evidence of precursor lesions. The medial lesions consisted of separation and fraying of medial fibers and/or foci of calcification.

Typical lesions will be illustrated by lantern slides.

38. Hypercholesterolemia in Monkeys Ingesting an Adequate Diet

George E. Cox, L. G. Nelson and C. Bruce Taylor

Department of Pathology, School of Medicine, University of North Carolina, Chapel Hill, N. C.

Hypercholesterolemia of 400 to 650 mg. per 100 cc. has been induced in adult male and female macacus Rhesus monkeys ingesting adequate diets. Five nearly isocaloric diets have been tested for periods of two to six months. Each diet supplied 30 per cent of calories as lipids and 3 Gm. of cholesterol per animal per day. Diets I and II contained bread, fruits and vegetables. Diet I also contained skim milk and vegetable oil. In diet II, cream with 15 per cent butter fat replaced the skim milk and vegetable oil of diet I. Diet III consisted of rice, butter, fruits and vegetables. Diets IV and V consisted of ground monkey food and butter. One egg yolk was added to diet V.

Diets I, II and III resulted in elevation of cholesterol levels from 125 mg per 100 cc. to nearly 300 mg. per 100 cc. While on these diets animals lost weight slowly.

Diets IV and V were more palatable and eaten more completely. Feeding these diets resulted in elevation of cholesterol levels from (150 to 275 mg. per 100 cc.) to (400 to 650 mg. per 100 cc.) within two months. All animals gained weight while on these diets.

39. The in Vitro Exchange of Phospholipid Phosphorus between Lipoproteins

Howard A. Eder, Joseph I. Bragdon and Edwin Boyle

Laboratory of Metabolism, National Heart Institute, National Institutes of Health, Bethesda, Md.

The alpha and beta serum lipoproteins of rabbits given P^{32} and of control animals were separated by ultracentrifugal flotation at a solvent density of 1.07 obtained either by addition of concentrated salt solution or D_2O. The specific activities of lipid phosphorus in the two fractions were almost identical.

Labeled beta lipoproteins were mixed with unlabeled alpha lipoproteins, and labeled alpha lipoproteins were mixed with unlabeled beta lipoproteins. After standing at various time intervals the lipoproteins in the mixtures were again separated. Exchange of P^{32} from one lipoprotein group to the other had occurred rapidly. Transfer was apparent within minutes and was almost maximal at three hours. Complete equilibration, however, was not reached even after 21 hours at room temperature. When $H_3P^{32}O_4$ was added to serum in vitro exchange with lipoprotein phosphorus did not occur.

These data suggest that both groups of plasma lipoproteins are active in phospholipid transport. It is evident that differences in the metabolism of the various lipoproteins cannot be detected by study of the metabolism of the phospholipids in the lipoproteins.

40. Atherosclerosis in the Intramural as Compared with Extramural Coronary Arteries

Joseph C. Edwards, Charles Burnsides, Richard Swarm and A. I. Lansing

Department of Medicine, Washington University School of Medicine, St. Louis, Mo.

Among 277 hearts examined in a series of autopsies, only 16 instances of intramural coronary arteries were observed. All but one of these had one intramural portion with atheromata and narrowing of the lumen. The other extramural coronary arteries in these hearts had atherosclerotic involvement also. Eight had marked involvement, five had

moderate, and two had slight arteriosclerosis. One was in the left circumflex branch and was occluded by a thrombus in the intramural portion. Eleven were in the left anterior descending branch; only one involved the right coronary artery. We found approximately 1 out of every 17 human hearts (5.8 per cent) had an intramural coronary for some portion of its proximal or mid course. Microscopic examinations, degrees of involvement and other data were analyzed. Elastic tissue studies were performed on some of the specimens. The data and questions relating to the problem will be discussed.

In these observations there was no evidence to support the concept (Geiringer, E.: The relation of the mural coronary artery to arteriosclerosis. Am. Heart J. **41:** 359, 1951) that covering of a coronary artery by heart muscle during all or a part of its main course protects the artery from degenerative abnormalities.

41. Studies of Arteriovenous Oxygen Differences in Atherosclerotic Individuals before and after Heparin

Hyman Engelberg and Robert Kuhn

Cedars of Lebanon Hospital, Los Angeles, Calif.

Arteriovenous oxygen differences were determined in 36 patients with atherosclerotic disease. Arterial blood was obtained from the femoral artery, venous blood from the antecubital vein under controlled conditions. Usually two to six control values were taken, many after placebos. In many studies hand flow was occluded so that only the more stable forearm blood was measured.

In the majority of patients following heparin, and not after oral anticoagulants, there was a 25 35 per cent increase in the arteriovenous oxygen difference with a gradual return in several days to control levels. These findings were due to increased tissue oxygen utilization and were not due to altered blood flow. Measurements of total basal oxygen consumption following placebos and heparin usually showed increased oxygen consumption after heparin. In a few patients anoxic T waves, not influenced by nitroglycerin, improved coincidentally with increased arteriovenous differences after heparin, and the anoxic pattern recurred after heparin was stopped, indicating that increased uptake of oxygen may also occur in the myocardium after heparin.

Several possibilities as to the mechanism of the effect observed will be discussed.

42. Correlation of Plasma Heparin Levels and Serum Low Density Lipoproteins

Hyman Engelberg

Cedars of Lebanon Hospital, Los Angeles, Calif.

Serum lipoproteins and plasma heparin levels were determined in 122 individuals. Ultracentrifugal analyses were performed at the Institute of Medical Physics, Belmont, and at the Donner Laboratory, University of California. Plasma heparin determinations, in duplicate, were made using the method recently described from this laboratory.

Calculation of the Pearson product-moment correlation coefficient, r, revealed an inverse correlation between measured heparin and Standard S_f 0–400 lipoproteins. For the correlation between plasma heparin and Standard S_f 0–12 lipoproteins $r = -0.21$, which, for 122 cases, is significant at between the 1 per cent and 2 per cent levels. For the correlation between plasma heparin and Standard S_f 12–400 lipoproteins $r = -0.146$ which is at the 10 per cent level of confidence and therefore not statistically significant, although it does show a continuous variation of the inverse type. These preliminary findings lend support to

he possibility that a deficiency of heparin production in the body is etiologically related to those lipid metabolic defects which are involved in the development of atherosclerosis.

43. Newer Clinical and Laboratory Studies in the Aged. IV. Atherosclerosis in Normal Patients 80 to 100 Years of Age

A. Allen Goldbloom, Harold B. Eiber, Irving Chapman, Otto Deutschberger and Walter R. Loewe

Medical Service of the New York Medical College, Flower and Fifth Avenue Hospitals (Bird S. Coler Hospital Division), New York, N. Y.

Seventy-five patients aged 80 to 100, with no previous metabolic, coronary artery or cardiovascular disease were studied; these patients were confined to a chronic disease hospital.

There are no published reports to date, in this age group of serum lipid partitions, S_f lipoprotein molecules, paper electrophoresis (including lipidograms), roentgenologic, ballistocradiographic and serial pathologic studies. Findings were compared and correlated with similar studies of younger patients (25 to 80 years).

There is a "threshold" between the ages 65 to 75 years, after which there is a decline of total serum lipid, S_f lipoprotein molecules, and atherogenic index. Total cholesterol and phospholipids shows no significant changes, with the ratio of phospholipid to total cholesterol (P/C ratio) being statistically inconclusive.

Paper electrophoresis showed little significant difference between the lipoprotein distribution in the young and old age groups. In the protein distribution, the albumin concentration and albumin-to-globulin ratios were less in the aged group. There is no correlation between the chemical lipid determinations, the S_f lipoprotein molecules, and the lipidogram by paper electrophoresis.

Six hundred and fifty routine chest films were surveyed for calcification of the thoracic aorta, including the seventy-five patients of this series. Calcification of the thoracic aorta progresses in the aged more rapidly in women than in men. Marked widening of the aortic notch is not associated with heavy calcifications in both sexes. Abdominal aorta studies are discussed.

Postmortem examinations of cross sections of the aorta at various levels show changes anticipated in old age groups. Ballistocardiograms were almost uniformly abnormal in the presence of 71 per cent normal electrocardiograms. Ophthalmoscopic examinations showed arteriosclerotic changes in most cases.

The significance of the findings of low serum lipid and S_f lipoprotein molecules values in this age group with marked roentgenologic thoracic calcification and microscopic pathologic atherosclerosis will be discussed.

44. Postmortem Studies of Serum Lipoproteins in One-Hundred Consecutive Autopsies

I. J. Greenblatt, V. A. Bradess and D. M. Spain

Beth-El Hospital and Westchester County Medical Examiner's Office, and Department of Laboratories and Research, Westchester, N. Y.

Antemortem blood samples were compared with postmortem blood samples taken at intervals after death to validate the study. The bloods were found satisfactory because little change was seen after 16 hours post mortem. All the bloods were mailed in for lipid and lipoprotein determinations.

Every subject was somatotyped according

to Sheldon's classification. The coronary arteries were dissected, and graded according to extent and degree of atheromata. The findings were compared with the atheroma in the aorta and with the serum lipids and somatotypes.

The source material of all the cases were those of the Medical Examiner's Office of Westchester County, N. Y. All subjects studied were those due to sudden death. Both sexes and an age group covering a 50-year span are included in this study.

45. The Effect of a Brain Extract on Endogenous Hypercholesteremia

Richard J. Jones, Eugene L. Balter and Sheldon Huffman

University of Chicago, Department of Medicine, Chicago, Ill.

The relative roles of dietary and endogenous cholesterol in the production of any hypercholesteremia have not been fully determined, but certainly an agent which effectively neutralizes cholesterol in the intestinal phase might be expected to effect both. Recently we have observed a salutary effect in two examples of experimental endogenous hypercholesteremia with the administration of a hot alcoholic extract of acetone-extracted beef brain.

Two groups of cockerels 10 weeks of age were given estrogen in their daily water allowance. One group was fed plain chick starter mash and 10 per cent cottonseed oil, the other received this plus 1 per cent cholesterol, for a period of 12 weeks. For the last six weeks, half of each group received a supplement of 10 per cent brain extract. In the group receiving no additional cholesterol, an unsustained reduction in the resulting hypercholesteremia was observed following the administration of the brain extract.

Four dogs with alloxan diabetes of long standing, maintained on a constant diet and the minimum dose of insulin required to prevent symptoms, had weekly serum cholesterol determinations for a 12-week period. Brain extract, 30 Gm. per day, given during the sixth, seventh, and eighth weeks, significantly reduced cholesterol levels.

46. Field Studies in Italy, 1954, on Serum Cholesterol and Lipoproteins, Coronary Heart Disease, and the Diet

Ancel Keys, Flaminio Fidanza, Paul Dudley White, Bengt Swahn and Margaret Haney Keys with the collaboration of Joseph T. Doyle, Haqvin Malmros, B. Bronte Stewart, Ratko Buzina, Gunnar Biörck, Ernest Klepetar, Gino Bergami, F. di Lorenzo, Arrigo Poppi, Teodoro Postelli and Robert Dale

University of Minnesota, Minneapolis, Minn., and the University of Naples, Italy

Measurements of total cholesterol and of alpha and beta lipoproteins in the serum, and of obesity and anthropometric characteristics, were made on 456 clinically healthy men, suitably distributed over ages 19 to 60 years, and representing sedentary, moderate and heavy work as follows: (1) 68 clerical workers in Naples, (2) 150 firemen in Naples, (3) 138 steel and foundry workers in Naples, (4) 46 prominent business and professional men in Naples, and (5) 54 policemen in Bologna. The results on the first three groups confirm and greatly extend the previously reported findings of low cholesterol levels in healthy well-fed men on habitual low fat diets. The results from the Neapolitan businessmen and the men of Bologna, whose diets are considerably higher in fats, were much more similar to findings in Minnesota. The relationships of lipoprotein lipid levels to total cholesterol in the serum will be discussed. Simultaneous comparative surveys of the incidence of heart disease, of coronary heart disease in particular, among other 2000 medical patients in genera

hospitals in Italy and in the United States will be summarized and the relationship of the results to the blood and other studies will be discussed.

47. The Presence of Succinic Dehydrogenase and of Krebs' Cycle Enzymes in Human Aortic Tissue

J. E. Kirk and T. S. Laursen

Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

Investigations were carried out on the dehydrogenase activity of human aortic tissue, using a quantitative tetrazolium technic. Experiments were performed under sterile conditions on 25 aortic samples. Annular segments of the thoracic aorta, consisting of the intima and media, were placed at 37 C. in a triphenyltetrazolium chloride-phosphate buffer solution, to which had been added glucose, lactate, pyruvate, acetate, or one of the intermediate compounds of the Krebs cycle in 0.15 M concentration. The formed formazan was extracted with acetone and determined spectrophotometrically.

A notable succinic dehydrogenase activity of the aortic tissue was found, an average of 0.182 mg. of formazan being formed by 1000 mg. fresh tissue per hour. The formazan formation without addition of substrate valued 13 per cent of the succinic dehydrogenase activity. For the remaining substrates the following rates of tetrazolium reduction were encountered, expressed in percentage of the formazan formation in succinate medium: Glucose 15 per cent, lactate 17 per cent, pyruvate 10 per cent, acetate 28 per cent, cis-aconitate 49 per cent, citrate 31 per cent, alpha-ketoglutarate 36 per cent, malate 23 per cent, and oxalacetate 27 per cent. Addition of malonate in 0.03 M concentration produced an 80 per cent inhibition of the succinic dehydrogenase activity.

48. Changes with Age in Diffusion Coefficients of Solutes for Human Aortic Tissue

J. E. Kirk and T. S. Laursen

Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

Determinations have been performed of the diffusion coefficients of various gases and non-gaseous solutes on 51 preparations of the intima (with attached subintimal tissue) and 50 preparations of the media of the human aorta. The ages of the individuals from whom the samples were derived ranged between 10 and 80 years. The measurements were carried out under sterile conditions by the procedure of S. G. Johnsen and J. E. Kirk

A tendency was observed for the diffusion coefficient values to increase with the age of the individuals. The coefficients of correlation between age and the diffusion coefficients were as follows for the intima samples: nitrogen, + 0.28 (t = 2.04); oxygen, + 0.18 (t = 1.27); carbon dioxide, + 0.23 (t = 1.66); lactate, + 0.46 (t = 3.60); iodide, + 0.38 (t = 2.89); and glucose, + 0.58 (t = 4.99). For the media preparations a similar tendency to an increase in permeability with age was noted, the correlation coefficients being: nitrogen, + 0 35 (t = 2.60); oxygen, + 0.29 (t = 2.08); carbon dioxide, + 0.36 (t = 2.67); lactate, + 0.41 (t = 3.12); iodide, + 0.39 (t = 2.93); and glucose, + 0.44 (t = 3.35).

49. The Interpretation of Tests of Peripheral Circulatory Function

Milton Landowne

Section on Gerontology, National Heart Institute, National Institutes of Health, Bethesda, and the Baltimore City Hospitals, Baltimore, Md.

Occlusive or restrictive disorders of the circulation are too often recognized only by the complicating sequelae of an inadequate blood supply. On the other hand, the circulation may remain functionally adequate despite considerable structural alteration such as tortuosity, hardening, and calcification of vessels. A convenient interpretable test of functional circulatory adequacy is therefore of great value, particularly in the older person. At rest the resistance to the flow of blood through the normal extremity is relatively high largely due to the mediation of arterioles and capillaries, and the blood flow is correspondingly low. In nonvasospastic arterial disease of the extremities, even if moderately advanced, the extreme adjustability of these smallest vessels provides compensation for an increased *arterial* resistance and a *normal net resistance and resting flow* may be maintained. When the arterioles and capillaries are adequately dilated, not only is their resistance markedly reduced but the proportional contribution of these vessels to the total resistance becomes much less, and a blood supply which remains relatively reduced under these conditions can more reliably be considered to be due to restrictive vascular disease. Thus the maximally dilated state indicates the basic capability of the vascular tree, against which the resting state may be compared as an index of conditions which prevail at a given time.

Skin temperature measurements offer no information about blood supply in other areas of distribution than skin and generalizations to major vessels require caution. It is to be recalled that environmental and blood temperatures limit the range of skin temperatures, and that equal stepwise reductions in blood flow result in progressively greater stepwise reductions in skin temperature.

50. Low Density Lipoproteins Versus Serum Cholesterol in Familial Hypercholesterolemia

Lena A. Lewis, A. C. Corcoran and Irvine H. Page

Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio

Serum lipoproteins were measured at a density of 1.21 in families of three patients who had shown high serum cholesterols.

Both parents in one family showed high concentrations of low density ($-S > 70$) and somewhat elevated $-S$ 40–70 fractions; respective total serum cholesterol concentrations were only 151 and 292 mg. per 100 ml. Of four sons, three showed lipoprotein distributions similar to the parents'; cholesterol was increased (> 300 mg. per 100 ml.) in only one.

In another family, the father's serum was normal, while the mother's (cholesterol, 289 mg. per 100 ml.) had high concentrations of low density lipoproteins ($-S$ 70 and 40–70) as did also one (cholesterol 277) of the two sons.

One man, who complained of xanthomatosis, had hypercholesterolemia (about 1000 mg. per 100 ml.) and very severe increases in low density lipoproteins. Among his eight children, aged 8 to 28, the highest cholesterol concentration was 260 mg. per 100 ml. in a girl, while two (both boys) showed concentrations of $-S$ 40–70 fractions excessive for their ages.

Thus, presence of increased amounts of low density lipoproteins is more common than frank hypercholesterolemia in those with a hypercholesterolemic trait.

These abnormalities when detected persist for long periods. Thus, in the last patient, observations over two years during treatment with a pancreatic extract (Lipotrop), an artichoke preparation (Solochol) and a "lipotropic" mixture (Monichol) showed no changes in lipoproteins patterns or serum cholesterol except falls of both to about two-thirds of the means of the remaining observations while taking Lipotrop.

51. Spontaneous Arteriosclerosis in Epinephrine-Thyroxin and in Cholesterol Induced Arteriopathy

Y. T. Oester, Oscar F. Davis and Bernard Friedman

Department of Pharmacology and Experimental Therapeutics, Stritch School of Medicine of Loyola University, Chicago, Ill.

Epinephrine and thyroxine were injected into 48 rabbits, to produce an essentially medial aortic sclerosis. This sclerosis rapidly developed in 6 to 15 days, and was of high incidence, approximately 90 per cent. Cholesterol in suspension, intravenously injected into 32 other rabbits, produced an essentially intimal aortic sclerosis. This was present in some 72 per cent of the animals after 15 to 20 days of such treatment. Gross observations of the aorta were the primary criteria used in these evaluations. In addition, microscopic examination of selected tissues were made. When these two sclerogenic regimens were combined in six surviving rabbits, that is the epinephrine-thyroxin and also the cholesterol injected concomitantly, arteriopathy resulted in all animals. Intimal sclerosis and proliferation with foam cell formation were common, and apparently of greater severity. The medial sclerosis was similar to that seen with epinephrine-thyroxin alone.

Seventy-one rabbits, not on any sclerogenic program, were examined for gross evidence of "spontaneous" aortic arteriopathy. Only one arteriosclerotic lesion of any type was found. Gross spontaneous arteriosclerosis does not appear to be a significant factor in this study of aortic sclerosis.

It was observed that intimal proliferation is also seen in some cases of medial sclerosis, produced solely by epinephrine-thyroxine. This lends some support to the belief that medial arteriosclerosis and intimal atherosclerosis are not entirely unrelated. Imbalance of one or of several factors in the metabolism of artery, perhaps induced by epinephrine and/or thyroxin dysfunctions, may well be a prerequisite or concomitant, not only of experimental arteriopathy, but also of clinical forms of arteriopathy as well.

52. The Demonstration of Iron in Early Atherosclerotic Plaques

J. C. Paterson and T. Moffatt

Westminster Hospital, Department of Veterans' Affairs and the Collip Medical Research Laboratory, University of Western Ontario, London, Ontario, Canada

Intimal hemorrhages are usually regarded as mere complications in the evolution of atherosclerosis, and therefore not of any etiologic significance. Recently, we have used a well-known histochemical procedure, the Prussian blue reaction for ferric iron, to show that deposits of iron (derived presumably from intimal hemorrhages) are extraordinarily frequent in the unfixed human aorta when it is exposed to the reagent and examined macroscopically. The deposits are confined exclusively to atherosclerotic lesions: they occur as pinpoint spots along fatty streaks, as diffuse discolorations in pearly plaques, and as

encircling masses in older lesions. They have been found in 20 year old subjects as well as in older individuals. The discolorations have been noted in 47 out of 50 aortas examined to date, the exceptions being a 14 year old boy and two women. They have been just as prominent in cases of sudden death as in patients with prolonged illnesses. Microscopically, the discolorations have a decided tendency to occur at points of vascularization, although blood within the capillaries does not give the reaction. It is concluded, tentatively, that the deposits result from the rupture of intimal capillaries. If true, then the leakage of blood into tissues is a characteristic feature in the development of atherosclerotic plaques; and if iron can be laid down at points of intimal hemorrhage, it is reasonable to assume that the lipid which is present in normal blood can be deposited at the same time.

53. Influences of Neutral Fat and Plant Sterols on Exogenous and Endogenous Hypercholesterolemia and Hyperphospholipemia in Chicks

Ruth Pick, Louis N. Katz, Simon Rodbard and Jeremiah Stamler

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Previous work from this department established the general principle that dietary factors may exert a significant influence upon the degree of hyperlipemia supervening in response to exogenous dietary cholesterol. The present experiments explored this problem further, and also investigated the ability of dietary factors to influence endogenous estrogen-induced hyperlipemia in cockerels. The data indicate: (a) In response to a fixed intake of cholesterol, degree of hypercholesterolemia and hyperphospholipemia tends to rise with increases in the neutral fat content of the diet. (b) When cholesterol is incorporated in a defatted mash, little or no hyperlipemia supervenes. (c) When ordinary chick starter mash is supplemented with cholesterol plus plant sterols or defatted brain extract, little or no hyperlipemia supervenes. (d) Feeding defatted mash has no inhibitory effect on endogenous estrogen-induced hypercholesterolemia and hyperphospholipemia. (e) Feeding plant sterols has no inhibitory effect on endogenous estrogen-induced hyperlipemia.

It is concluded: Diets free of neutral fat or supplemented with plant sterols are both capable of preventing the hypercholesterolemia ordinarily developing in response to cholesterol feeding. However, none of these diets suppresses endogenous estrogen-induced hypercholesterolemia and hyperphospholipemia.

54. Four Years Preliminary Review Clinic for the Study of Arteriosclerosis

Paul B. Roen, M.D., Ernest W. Townsend, M.D., John W. Perry, M.D.

Hollywood Presbyterian Hospital, Hollywood, Calif.

In a degenerative disease such as atherosclerosis where it usually takes a good proportion of the latter half of a man's life to develop, four years is a short time in which to make a clinical report. However, information obtained in this study may eventually prove to be facts.

So far the hereditary tendency has been demonstrated. The variability of the serum lipids in various diseases and the stability or instability was noted. Also for the initial determination of serum lipids, age, sex and ratio has been compiled. Some information relative to certain diseases was obtained. The efficiency of the low lipid diet in a percentage of the patients over one years time was proved. There has been some correlation between serum lipids, chylomicrons, micromicrons and the large lipoprotein molecules as demonstrated by Gofman. The value of repeated eye

ground examinations and fundus photography is discussed. A report on mortality statistics and postmortem tissue is interesting.

From this study our present general views of the management of atherosclerosis will be given. A therapeutic approach to atherosclerosis is outlined. Our experience is related as to what may be expected from therapy.

55. The Relationship of Essential Hyperlipemia to Premature Atherosclerosis

Alfred Soffer and Martin Murray

Laboratories of the Genesee Hospital, Rochester, N. Y.

The evidence presented illustrates that premature atherosclerosis is found in essential hyperlipemia and that when present it is associated with hypercholesterolemia. This is perhaps one more link in the chain of observations which has placed such a heavy burden of incrimination upon cholesterol in the family of circulatory diseases. These findings prompt us to state that contrary to previous concepts it is no longer tenable to believe that essential hyperlipemia is a benign disease.

Seven essential hyperlipemia patients with an average age of 46 years were studied for an average period of two and one-half years. Resting electrocardiograms, exercise electrocardiograms, ballistocardiograms and skin temperature responses were obtained throughout this interval. Four of these subjects manifested objective and subjective evidence of premature atherosclerosis. Repeated serum lipid analyses in these patients and in normal controls after specific dietary or total caloric restrictions revealed a relatively static blood picture when viewed in terms of years rather than months. Intravenous heparin produced dramatic though transient lowering of total lipids but this is due predominantly to its action upon neutral fat since cholesterol and phospholipids showed only minimal changes. The prolonged use of heparin as a therapeutic agent was studied and though no certain effect can be attributed to this therapy further study in this direction is warranted. The turbidity index described in Moreton Units is a means of determining quantitatively the changes in chylomicrons, but the biochemical determination of serum neutral fat permits the observation of the same trends. A dispersing property of heparin could produce the changes in ultracentrifugal and chylomicron values, but there is no explanation at this time for the absolute decrease in neutral fat following heparin administration. Heparin produced no consistent effect upon the cholesterol-phospholipid, free cholesterol-phospholipid, or cholesterol esters-cholesterol ratios.

56. Hemorrhagic Lipemia and the Production of Clearing Factor in Rabbits

John J. Spitzer

Department of Physiology, Florida State University, Tallahassee, Fla.

Heavy loss of erythrocytes due to repeated bleedings, or any other cause, results in marked increase in serum lipids and visible lipemia in the rabbit. The immediate cause of fat mobilization in these animals is not entirely understood.

There is a constantly increasing body of data indicating the important role of heparin (or of the heparin-produced lipemia clearing factor) in influencing fat metabolism. In view of that, the present study was undertaken to investigate the possible causal relation between the ability of an animal to produce clearing factor (C F) and the development of hemorrhagic lipemia.

Fourteen rabbits were used in the first group of experiments. Before any treatment, some of the rabbits were tested for their ability to produce clearing factor. All of the latter animals produced clearing factor after the injec

tion of 0.6 to 2.0 mg. heparin. Sera were tested in vitro for the presence of clearing factor by incubation with coconut oil emulsion. The presence of clearing factor resulted in clearing of the emulsion as measured by a Coleman Junior Spectrophotometer. The rabbits were then bled (15 to 30 ml. per day, for 3 to 19 days) until they developed visible lipemia. Their ability to clear lipemia and to produce clearing factor after an injection of heparin was tested again. In all, but one animal, 0.6 to 2.0 mg. heparin produced in 10 minutes little or no clearing of lipemia in vivo. No clearing factor activity could be found in vitro in the sera of all, but one animal, although the clotting time of the blood was noticeably prolonged after the injection of heparin. Most of the postheparin sera became turbid after several hours at room or at refrigerator temperature. When these animals were left to recover for a few days, they again were able to produce clearing factor after the injection of heparin. Their postheparin sera cleared coconut oil emulsion in vitro.

The second part of the problem was whether this altered reaction of rabbits showing hemorrhagic lipemia develops gradually or occurs suddenly together with the appearance of visible lipemia. In one approach to this question 11 rabbits were bled (16 to 25 ml. per day, for 5 to 14 days) to the stage where they became anemic, but visible lipemia had not yet developed. Injections of 0.6 to 2.0 mg. heparin invariably produced clearing factor in these animals; that is, their sera cleared coconut oil emulsion in vitro. Another approach to the same question was as follows. Normal rabbits usually do not show alimentary lipemia, not even after a fatty meal. If, however, rabbits were bled to the point where they become anemic, but not lipemic yet, they exhibit visible lipemia after a fatty meal. Three rabbits were bled 21 to 27 ml. per day, for 3 to 10 days. They were fed cod liver oil with their food and after showing visible lipemia, 0.6 to 2.0 mg. heparin was injected which produced a marked clearing of lipemia.

It seems on the basis of the above experiments that the appearance of visible lipemia in hemorrhagic rabbits occurs at the same time when the ability of the animal to produce clearing factor becomes altered. The broader pathologic importance of the above findings is being investigated.

57. Dietary and Hormonal Influences on Hepatic Cholesterol Synthesis in Chicks

Jeremiah Stamler, R. Gordon Gould and C. Bolene-Williams

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.; and the Los Alamos Scientific Laboratory, University of California, Los Alamos, N. M.

Utilizing C^{14}-labeled acetate as tracer, a survey was made of the effects of chronic cholesterol feeding and chronic steroid hormone administration on hepatic cholesterol synthesis in cockerels. The feeding of a diet supplemented with 1 per cent cholesterol plus 5 per cent cottonseed oil resulted in marked hypercholesterolemia and hepatic cholesterosis, with practically complete suppression of liver cholesterol synthesis and resultant absence of newly synthesized cholesterol in plasma. This cessation of hepatic cholesterol synthesis was also observed in chicks fed mash supplemented with both cholesterol and desiccated thyroid.

Chronic exhibition of estrogens to cockerels on a diet of unsupplemented chick starter mash induced slight hepatic cholesterosis and marked hypercholesterolemia, associated with a threefold increase in the total of newly synthesized cholesterol in liver and plasma. Chronic administration of hydrocortisone also effected slight hepatic cholesterosis and marked hypercholesterolemia, accompanied by a moderate increase in the total of newly synthesized cholesterol in liver and plasma.

It is concluded that: (1) the chick, like other species previously studied, responds to cholesterol feeding with cessation of hepatic cholesterol synthesis; (2) both estrogens and

hydrocortisone increase hepatic cholesterol synthesis in cockerels; (3) increased hepatic cholesterol synthesis is apparently a significant factor in the mechanism of steroid-induced endogenous hypercholesterolemia in this avian species.

58. Atherosclerosis in Areas of Vascular Injury in Monkeys with Mild Hypercholesterolemia

C. Bruce Taylor, G. E. Cox, B. J. Hall-Taylor and L. G. Nelson

Department of Pathology, School of Medicine, University of North Carolina, Chapel Hill, N. C.

Atherosclerosis has been induced in Rhesus monkeys with serum cholesterol levels below 350 mg. per 100 cc. Localized vascular injuries were produced by freezing. Control animals (serum cholesterol, 125 mg. per 100 cc.) showed excellent intimal scars, free of lipids, at sites of injury. Ten to 16 weeks after freezing, lesions of mildly hypercholesterolemic monkeys (range 175 to 350 mg. per 100 cc.; average, 250 mg. per 100 cc.) showed localization of lipids in poorly formed intimal scars. Uninjured areas showed no atherosclerosis.

These data suggest new concepts concerning pathogenesis of human atherosclerosis, widely observed with serum cholesterol levels below 350 mg. per 100 cc. The "milking" action of systolic stretching and diastolic contraction of normal, resilient, arterial walls may play a major role in movement of their interestitial fluids. This "milking" action is temporarily lost following injury, and its restoration is dependent upon elastic properties of repairative intimal scars.

Mild hypercholesterolemia probably does not cause lipid deposition in normal arterial walls but may, at sites of injury such as those produced by freezing. It appears to impair arterial repair (a continuous process in man) resulting in inelastic, intimal scars which fix arterial walls in extension; with loss of "milking" action, interstitial edema with lipid deposition is observed in mild hypercholesterolemia.

59. Serum Cholesterol Concentration and Ballistocardiographic Characteristics of Middle-Aged Men

Henry Longstreet Taylor and Joseph T. Anderson

Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

Seven serum cholesterol determinations, made annually on 184 clinically healthy business men, were averaged for each man. The group was arranged in quintiles of cholesterol concentration. The mean difference in the cholesterol concentration between the first and fifth quintiles was 98 mg. per 100 ml. The IJ forces of three records obtained annually with the low frequency, critically damped ballistocardiograph were averaged for each of the 184 men. The mean IJ force for each quintile of the cholesterol concentration distribution was calculated. The difference of 3.1 Gm. between the first and fifth quintile was not statistically significant. In subgroups of 111 men with ballistocardiographic patterns typical of youth and 73 with atypical ballistocardiograms, there was no difference in IJ force between high and low serum cholesterol concentration groups. Two high frequency (Starr) ballistocardiographic records were obtained on these subjects a year apart. It was found that the abnormal patterns were distributed evenly throughout the quintiles of cholesterol concentration. It is concluded that high serum cholesterol concentrations in middle-aged men are not associated with abnormal patterns in the high frequency ballistocardiographic record or small IJ forces calculated from the low frequency, critically damped ballistocardiographic record.

60. Plasma Lipids and the Arterial Wall

L. L. Waters

Department of Pathology, Yale University School of Medicine, New Haven, Conn.

Chylomicrons and lipoproteins of normal human plasma were introduced into arteries of dogs either by injection into the vessel wall, by placing the material into the lumen of a doubly-ligated arterial segment, or by combining intravenous injection of the lipid with allylamine injury of arteries. The arterial lesions resulting from these procedures and the fate of the deposited lipids were compared

Placed in the vessel wall, ether-extracted plasma fat or chylomicrons gave rise to foam-cellular lesions. Certain features of atheroma in man are reproduced. Plasma lipoprotein under the same conditions rapidly disappeared from the injection site.

Chylomicrons placed in ligated carotid loops outside the body at physiologic pressures did not infiltrate the artery wall in three hours. In the same experiment, with endothelial damage, infiltration was demonstrable and was proportional to intravascular pressure and time. Soluble lipoproteins infiltrated without microscopically visible endothelial damage. In ligated carotid loops in the body, chylomicrons localized massively in the vessel wall if endothelial damage was present, less if it were absent. Lipoprotein showed less tendency to localize under these conditions.

Injected systemically, both chylomicrons and soluble lipoproteins localized in areas of arterial injury associated with allylamine administration, and gave rise to foam-cellular lesions. Whereas chylomicrons were deposited immediately as sudanophilic droplets, lipoproteins stained diffusely and thereafter showed progressive alteration to droplet formation, and foam-cellular accumulation.

61. Atheromatous Hypertension—A Clinical Entity. Diagnosis and Management

Joseph B. Wolffe

Department of Medicine, Valley Forge Heart Institute and Hospital, Fairview Village, and Wolffe Clinic, Philadelphia, Pa.

Hypertension has been noted in 27 per cent in a series of 1000 cases of clinically proven atherosclerotic cardiovascular disease. This type of hypertension is usually benign. In some cases there are periods of severe hyperpiesis with remissions.

This syndrome appears as a result of impaired circulation in segments of the kidney due to arterial obstruction. As shown by Janeway in 1909 and Goldblatt in 1934, there is one variety of hypertension which is due to some substance excreted by an ischemic kidney. Our findings suggest that atheromatous hypertension may be a subdivision of the "renal ischemic" variety which is further to be differentiated from so-called "renal hypertension."

Atherosclerosis will be briefly defined and differentiated from other common arteriopathies based upon the "Tentative Classification of Arteriopathies" of the American Society for the Study of Arteriosclerosis.

The relationship of cholesterol blood levels to S_f 10–20, cholesterol phospholipid ratio and renal studies in the diagnosis of atheromatous hypertension will be discussed.

Encouraging results have been obtained in atheromatous hypertension by treating the metabolic factors with pancreatic extracts, low fat diet, the alleviation of stressful situations and emotional conflicts.

A polypharmaceutical approach to the problem will be discussed. The value of sedatives and a variety of sympathicolytic drugs whenever indicated will be shown.

The presentation will be limited to personal experiences with patients at the Valley Forge Heart Institute and Wolffe Clinic without a general review of the literature.

62. The Phospholipids of the Plasma Lipoproteins

J. M. Steele, H. J. Kayden, B. B. Levy and H. Appleton

Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, New York, N. Y.

By differential hydrolysis of the phospholipids of the plasma and subsequent analysis of the fractions for choline by precipitation with KI_3, the proportion of lecithin and sphingomyelin were measured and the remaining phospholipids calculated by difference from the total phosphorous.

This procedure was carried out in 41 normal individuals and 43 patients with a variety of diseases.

The normal average for lecithin was found to be 2.03 ± 0.11 micromols per milliliter, for sphingomyelin 0.38 ± .01, for the non–lecithin-containing phospholipids 0.45.

Marked elevation of the total phospholipids was found in nephrosis and biliary cirrhosis. In acute rheumatic fever the total phospholipids were low. In each case lecithin appeared to be more variable than the sphingomyelin.

Some studies have now been carried out and the alpha and beta lipoproteins separated by electrophoresis in a starch block. It appears that the ratio of lecithin to sphingomyelin is lower and more constant (3.0 to 3.5) in the beta than in the alpha lipoproteins (6 to 10).

63. Femoral Arteriography in Arteriosclerosis Obliterans

Charles M. Greenwald, Fay A. LeFevre and Victor G. deWolfe

Departments of Radiology and Medicine, Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio

Femoral arteriography is not a new examination. Until recently, however, employment of this study in the examination of patients with peripheral vascular disease has not been a routine diagnostic procedure. With the advent of new surgical procedures, particularly arterial graft, femoral arteriography has assumed new interest, particularly in the diagnosis of segmental occlusions.

This paper describes a technic of femoral arteriography which we believe incorporates several new ideas resulting in consistently good arteriograms. The results of 129 arteriograms in 91 patients are summarized.

Arteriography is the only examination demonstrating segmental arterial occlusion. It determines whether or not a patient is a suitable candidate for arterial graft. Femoral arteriography is a helpful study in determining the level of amputation and is one of the most reliable examinations in determining whether or not amputation should take place above or below the knee. The arteriograms in this study have also been correlated and studied with particular reference to the following: (1) level of vessel filling, (2) occlusion without refilling, (3) intimal disease only, (4) segmental block. A careful evaluation of the arteriogram, keeping in mind the above criteria, is of great aid in determining the patient's prognosis.

ABSTRACTS

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AVITAMINOSIS

Meneely, G. R., Tucker, R. G., Darby, W. J., and Auerbach, S. H.: Chronic Sodium Chloride Toxicity: Hypertension, Renal and Vascular Lesions. Ann. Int. Med. **39:** 991 (Nov.), 1953.

Purified rations, containing from 0.01 per cent to 9.8 per cent of sodium chloride, and water were fed at will to male albino rats from the age of 5 weeks. Diets both high and low in sodium chloride reduced the rate of growth. Water consumption was related directly to the amount of salt in the diet. A low-sodium diet depressed the appetite, but diets high in sodium chloride did not. Edema developed in 18 per cent of the rats eating the diets which contained from 7.0 per cent to 9.8 per cent of NaCl. Pathologic lesions were observed in the kidneys and to a lesser extent in various other tissues of rats consuming these high levels of salt. Concurrently, the animals developed anemia, lipemia, hypoproteinemia and azotemia. Sustained arterial hypertension was observed in the rats eating high levels of sodium chloride after nine months of the dietary regimen. A linear relationship was found to exist between the NaCl concentration in the diet and the systolic blood pressure.

WENDKOS

BACTERIAL ENDOCARDITIS

Brunson, J. G.: Coronary Embolism in Bacterial Endocarditis. Am. J. Path. **29:** 689 (July), 1953.

The writer records the results of his examinations of the coronary arteries and the myocardium in nine successive cases of bacterial endocarditis. All but one showed gross scars of varying size, and two of them showed fresh infarction. Microscopically, almost all showed infarcts, old or recent, embolism within small branches of the coronary arteries, and in two cases, there were calcific granulomas. None of the vessels showed significant atherosclerosis, and while five of the nine cases showed rheumatic valvular lesions, the author considered the larger scars to be of embolic origin. In one case, cortisone therapy was associated with striking septic emboli and infarction. There were no constant or diagnostic changes in the electrocardiograms. Sudden death occurred in five cases.

GOULEY

Beck, C. A.: Subacute Bacterial Endocarditis in Penicillin-Sensitive Patient. J.A.M.A. **153:** 1170 (Nov. 28), 1953.

A 49 year old patient, sensitive to various penicillin preparations, was successfully treated, without reaction, for subacute bacterial endocarditis by a combination of one million units of penicillin and 10 mg. chlorprophenpyridamine (Chlor-Trimeton) maleate per injection. The result is significant since other antibiotics failed to achieve the desired clinical response and because of the severity of the previous penicillin reaction.

KITCHELL

BLOOD COAGULATION

Dedichen, J.: Long-Term Anticoagulant Treatment of Cardiovascular Disorders with Phenylindanedione (Pid-Trombantin). Scandinav. J. Clin. & Lab. Invest. **5:** 324 (No. 4), 1953.

The long-term treatment of 55 ambulatory patients with phenylindanedione (Pid-Trombantin) is described. These patients were treated for six months or longer. In 37 patients, the dosage required was constant for two months or more and in six patients the dosage was constant for 12 months or more. The dosage was controlled by determination of the Proconvertin and prothrombin values. The necessary dose ranged between 50 and 22[illegible] mg.

daily. Fifteen patients showed an increasing tolerance of the drug, necessitating an increase in the dosage. This increasing tolerance appeared early in some patients and after several months in others. Three serious complications appeared in the first cases treated; these included severe intraperitoneal bleeding in one patient and gross hematuria in two others. Of 33 patients with angina pectoris, the pain was diminished in 26 and unchanged in the remaining seven. Of 22 patients with obliterating arterial disease, all but one showed symptomatic improvement and some became symptom-free. The dosages of dicumarol and phenylindanedione are not interchangeable.

ROSENBAUM

CONGENITAL ANOMALIES

Esclavissat, M., Puech, P., and Limon Lason, R.: Tetralogy of Fallot with Interatrial Communication. Arch. mal coeur **46:** 1109 (Dec.), 1953.

The authors studied five cases of so-called Pentalogy of Fallot. The diagnosis was made on the basis of catheterization data and confirmed by angiocardiography, surgery or, in three cases, by autopsy.

Clinically, cyanosis is intense with abrupt appearance and, as a rule, associated with squatting. Roentgenologically, a concentric type of right ventricular hypertrophy is found with diminution of pulmonary vascularity. In two cases the aorta was dextroposed. The finding of concomitant left ventricular hypertrophy is important, but its proof is extremely difficult. The electrocardiogram shows marked right heart strain, sometimes incomplete right bundle-branch block and abnormal "congenital" P waves.

As in the ordinary tetralogy, right ventricular pressures approach the systemic pressure, depending on the degree of overriding of the aorta. Gasometric analysis reveals that right-to-left shunts occur at two different levels. In one case with marked overriding of the aorta, desaturation was demonstrated to be present in the left atrium. In three other cases, the calculated magnitude of the ventricular shunt was negligible. Thus, of the two veno-arterial shunts, the atrial shunt appears to be the more important one in the production of peripheral desaturation.

PICK

Kattus, A. A., and Muller, W. H. Jr.: Patent Ductus Arteriosus with Reversal of Blood Flow. Report of a Successful Surgical Closure and Physiologic Studies. Ann. Surg. **138:** 870 (Dec.), 1953.

The purpose of this communication is to present a case report of a 36 year old man in whom a large ductus with reversal of blood flow, was successfully closed. No previous successful surgical closure of this type of ductus has been reported in the literature.

The authors believe that it is unlikely that every patent ductus with reversal of flow is suitable for closure. The decision apparently rests on three factors: (1) the degree of pulmonary resistance, whether this resistance is fixed, and whether it is reversible; (2) the reserve of the right ventricle; and (3) the degree of polycythemia. It is postulated that the size of the ductus may be of crucial importance in determining whether the patients develop pulmonary hypertension and reversal of flow. Apparently, the only way one can tell with certainty whether closure is possible is to occlude the ductus temporarily and observe the action of the heart. Marked tachycardia may develop when the ductus is clamped. After being clamped and released several times, the ductus may be finally clamped without producing change in rate or rhythm of the heart. If the ductus will not tolerate complete occlusion, an alternative is to anastomose the left subclavian artery to the left pulmonary artery, thus creating a much smaller ductus than the congenital one. One might then be able to divide the ductus completely.

DENNISON

Shumacker, H. B. Jr., Moore, T. C., and King, H.: The Experimental Closure of Atrial Septal Defects. J. Thoracic Surg. **26:** 551 (Dec.), 1953.

The object of this study was to explore various methods for surgical closure of apical septal defects and, if possible, to develop a method applicable to human patients. It was the authors' feeling that the ideal procedure for use in patients would be one which would be applicable to all types and sizes of atrial septal defects, would give fairly certain assurance of complete closure of the defect, preferably with autogenous tissue, and one which could be accomplished in the dry field without loss of blood, interference with cardiac function, without the necessity of using anticoagulants, and without the hazard of air embolism or intracardiac thrombosis.

Healthy, mongrel dogs were used. A large atrial septal defect, made through the open dry atrium during momentary occlusion of venous inflow, was created in each animal either immediately before the closure or at some time previous to it. Following induction of intravenously administered pentobarbital sodium, intratracheal ether-oxygen anesthesia was employed, using an intermittent positive pressure apparatus. The heart was exposed through a long right intercostal incision. Penicillin was given postoperatively for the first week. No anticoagulants were used.

The experiments with direct application of overfolded segments of atrial appendage or of pericardium demonstrated that such grafts are entirely suitable in the dog, unite firmly with the septum, and do not cause intracardiac thrombosis.

The experiences with the use of a rubber-capped glass chamber introduced into the base of the appendage showed this method to be safe and unattended by hazard of air embolism or intracardiac thrombosis. The position of the chamber somewhat distant from the defect resulted in some difficulty with accurate placement of sutures and suggested the likelihood that fixation of a larger chamber in the atrial wall near the defect might overcome this trouble.

The technic involving the use of an invaginated pericardial pocket gave satisfactory results and, after the most careful evaluation, seemed entirely suitable for use in human beings. It appeared to fulfill the following requirements of the ideal operation: it does not interfere with cardiac function; it is accomplished in a dry field without loss of blood; it uses autogenous tissue; it permits direct suture of graft to the rim of the defect; it entails no need for anticoagulants; and it seemingly is without danger of intracardiac thrombosis or air embolism.

Experience with one patient, however, has demonstrated that the pericardial pocket, when placed over a large defect, may be resorbed and literally melt away. Experiments are now under way in which the same technic is being employed utilizing a pocket of inert plastic material instead of pericardium.

DENNISON

Fry, W.: Herniation of the Left Auricle. Am. J. Surg. **86:** 736 (Dec.), 1953.

The author reported a case of herniation of the left auricle through a defect in the pericardium. The original diagnosis, based on the x-ray finding of an abnormal shadow in the region of the conus arteriosus, was that of a mediastinal mass. At operation, the auricular appendage of the left atrium was found to be in the pleural cavity. Since it was decided that the defect in the pericardium was congenital and since the patient had been asymptomatic, no attempt was made to repair the defect.

ABRAMSON

Souliè, P., Bouvrain, Y., Di Matteo, J., and Rey, C.: Pulmonary Tuberculosis in Congenital Cardiopathies. Arch. mal coeur **46:** 1057 (Dec.), 1953.

On the basis of 30 observations, the authors studied the incidence and course of pulmonary tuberculosis in congenital heart disease. In 24 cases having both diseases, the diagnosis of the malformation was established by cardiac catheterization or confirmed by surgery. Half of these cases were tetralogies, the others had atrial septal defects with or without pulmonary stenosis, and patent ducti; one had tricuspid atresia.

Open pulmonary tuberculosis is about 20 times as frequent in congenital heart disease as in the general population, and three to four times as frequent in patients with reduced pulmonary flow as in patients with normal pulmonary flow. In general, the prognosis is more serious in the former category. It would appear, therefore, that pulmonary hypovascularization constitutes a factor favorable for the development of pulmonary tuberculosis. A Blalock or Brock operation seems to arrest the pulmonary process in certain cases. On the other hand, closure of a patent ductus or an atrial septal defect may have an adverse effect and should be avoided under such circumstances.

PICK

Uyttenhove, Ph., Pannier, R., Van Loo, A., Vuylsteck, K., and Blanquaert, A.: Aberrant Pulmonary Veins. Act. cardiol. **8:** 594 (Fasc. 6), 1953.

The authors present case histories and laboratory data of four cases with anomalous drainage of the pulmonary veins. In each instance the anomaly was associated with other congenital lesions, such as an atrial septal defect, pulmonic stenosis, Fallot's tetralogy or tricuspid atresia. In three cases at least one pulmonary vein drained into the right atrium, in the case with tricuspid atresia into the superior vena cava.

In all cases the complete diagnosis was established by cardiac catheterization, during which the sound was seen to enter the anomalous vessel directly from the right border of the heart. In this way the possibility of passage of the catheter through an atrial communication into a pulmonary vein was excluded. Pathophysiologic and clinical aspects of anomalous pulmonary veins are discussed on the basis of hemodynamic data obtained in these four cases. The importance of a correct diagnosis is emphasized with respect to possible surgical correction of the lesion.

PICK

Andersen, J., and Nyfos, L.: Hypoplasia of the Aorta. An Autopsied Case. Acta. med. scandinav. **146:** 325 (Fasc. 5), 1953.

Hypoplasia of the aorta is a condition in which the lumina of the arterial vessels of the systemic circulation remain abnormally small and the walls abnormally thin and delicate. The heart may be diminished in size or may undergo compensatory hypertrophy and dilatation, particularly involving the left ventricle. Even though occurring as an isolated disorder, it is apt to lead to cardiac failure and is said to have always a doubtful prognosis. The authors describe a man, aged 22 years, who died of cardiac failure which had developed gradually over a period of seven or eight years. The blood pressure was always normal. Autopsy disclosed enormous hypertrophy of the heart and universal narrowing of the aorta. The clinical picture was that of increasing cardiac failure, progressive cardiac enlargement, the appearance of systolic and diastolic apical murmurs and increasing cyanosis. The heart weighed 1000 Gm. There was hypertrophy of both the right

and left halves of the heart but particularly of the left ventricle. The valves were normal. The aorta was extremely narrow throughout its entire course but especially in the aortic arch as far as the isthmus; it would admit only the index finger. The pulmonary artery was normal. The structure of the aortic wall was normal although the intima was slightly thickened in some areas. The only other evidence of congenital anomalies in this patient was pronounced fetal lobulation of both kidneys. The authors express the opinion that the hypertrophy of the heart seen in these cases is due to the increase in frictional resistance when the blood passes through the narrow aorta. This disorder should be included in the differential diagnosis in obscure cases of cardiac enlargement in young persons who present none of the usual signs of other forms of heart disease.

ROSENBAUM

Baffes, T. G., Johnson, F. R., Potts, W. J., and Gibson, S.: Anatomic Variations in the Tetralogy of Fallot. Am. Heart J. **46:** 657 (Nov.), 1953.

Forty-two specimens of tetralogy of Fallot available to the authors were classified into groups with relatively similar infundibular anatomy, with a view to evaluating the relative applicability of intracardiac infundibular resection and the shunt operations to each of these groups. Eighty-two per cent of this series was comprised of hearts taken from children under three years of age. The hearts most amenable to surgery comprised 19 per cent of the series; the pathology consisted of a bandlike stenosis at the lowest portion of the infundibulum associated with a dilated infundibular chamber above the point of obstruction. In 17 per cent of the patients, surgery was possible, but certain anatomic features could complicate the procedure. These patients had a subvalvular or intermediate stenosis. Sixty-four per cent of the series comprised those least amenable to surgery. These hearts consisted of either (1) an atretic pulmonary artery with the infundibulum sealed off from the lungs by obliteration of the pulmonary artery at the base of the heart; (2) a tubular stenosis of such severe degree that the entire crista supraventricularis would have had to be removed, or (3) a heart in which it would have been necessary to increase the size of the defect in the split crista supraventricularis or to remove the lower portion of the infundibulum.

RINZLER

CONGESTIVE HEART FAILURE

Fish, D. J., and Dillon, J. A.: Symptoms of Depression in Cardiac Failure, Report of a Case. New England J. Med. **249:** 493 (Sept. 17), 1953.

A 43 year old woman, whose chief complaint was extreme nervousness, is described. There was a history of intense environmental stress with symptoms of fatigue, exhaustion with slight exertion, dyspnea frequently occurring at night, and frightening dreams. Careful questioning also elicited a history of angina pectoris and orthopnea. It was learned that the patient had consulted four physicians previously over a period of one and one-half years and had been told she had a murmur of no particular significance. On this occasion, the patient first consulted a psychiatrist but because of the symptoms she was referred to an internist. A diagnosis of aortic stenosis, angina pectoris and left ventricular failure was made. Appropriate treatment was followed by prompt relief of the symptoms of depression, anxiety and tension. The importance of careful review of all symptoms, a careful physical examination, and the proper integration of psychiatry in medicine is emphasized.

ROSENBAUM

McVay, L. V., Sprunt, D. H., and Stern, T.: Antibiotic Prophylaxis in Chronic Congestive Failure. Am. J. M. Sc. **226:** 491 (Nov.), 1953.

For 20 months the authors administered Aureomycin and placebo capsules alternately to 175 patients with chronic congestive failure. The purpose of the study was to determine the effect of antibiotic prophylaxis upon the course of chronic cardiac disease. During the course of observations the effect of treatment upon bacterial flora and their resistance was examined and studies were performed relevant to hepatic, renal, and cardiac function. During the study intervals there were 34 deaths, 15 in the Aureomycin group and 19 in the placebo group. A definite reduction in respiratory infections was noted in the antibiotic group. Bronchopneumonia was the cause of death in four persons from the control group and one in the Aureomycin series. The incidence of respiratory infections, considered a great hazard to congestive failure patients was markedly reduced in the Aureomycin series. Subjectively, 36 patients in the Aureomycin group felt better contrasted to 23 of the controls. An increased appetite in 14 of the Aureomycin group resulted in improved strength, energy and interest in life. The sedimentation rates were lowered and hematocrits increased in the treated group. During the first week, four patients developed nausea and vomiting; it was found that three of these were receiving the placebo rather than Aureomycin. Mild to moderate diarrhea occurred in six patients receiving Aureomycin, pruritis ani in four. Otherwise, the side effects noted in the two groups were of equal incidence and in no case was it necessary to discontinue treatment. Of the liver function tests, the Bromsulphalein retention and flocculation tests showed improvement during the treatment with Aureomycin but not with placebo. The microbiologic studies disclosed no significant differences in the stool flora of the two groups of patients. The use of Paraben in the Aureomycin capsules appeared to prevent the overgrowth of yeasts previously noted with Aureomycin therapy. The authors conclude that prolonged anti-

biotic therapy may be of value in chronic congestive failure. The dosage employed in their study was 250 mg. of Aureomycin before breakfast and supper.

SHUMAN

Dimitroff, S. P., Griffith, G. C., Thorner, M. C., and Walker, J.: Clinical Evaluation of Gitalin in the Treatment of Congestive Heart Failure. Ann. Int. Med. **39:** 1189 (Dec.), 1953.

Amorphous Gitalin was used in the treatment of 68 patients with congestive heart failure of varying causes, degrees and duration. It was found to be effective in initial digitalization, redigitalization and maintenance digitalization of these patients. Case reports are presented to demonstrate the value of Gitalin in promptly and safely establishing digitalization and control of heart failure in eight patients in whom digitalis, digitoxin and Digoxin were ineffective, due to toxicity. No toxicity from Gitalin was encountered in any patient studied in this series. This can be attributed to the wide difference between the toxic and therapeutic dose of this particular cardiac glycoside. The average digitalizing dose was found to be 6.0 mg. and the daily maintenance dose to be 0.5 mg.

WENDKOS

CORONARY ARTERY DISEASE

Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., and Parks, J. W.: Coronary Heart-Disease and Physical Activity of Work. Lancet **6795:** 1053 (Nov. 21), 1953; **6796:** 1111 (Nov. 28), 1953.

The relation of physical activity or inactivity in work to coronary heart disease among middle-aged men was investigated by means of massive statistical data which was derived mainly from governmental and company medical records.

Transport workers, postal workers and civil service executive officers and clerks were observed over a one-year period. Bus conductors (on double-decker vehicles) were found to have less coronary heart disease than bus drivers; and postmen less than telephonists, executive officers and clerks. Moreover, what disease the conductors and postmen had was less severe.

On the basis of these observations, the hypothesis was advanced that men in physically active jobs have a lower incidence of coronary heart disease in middle age than men in physically inactive jobs. More important, the disease was not so severe in physically active workers, tending to be present first as angina pectoris and other relatively benign forms, and to have a smaller early case-fatality and a lower early mortality rate.

This hypothesis was tested by statistical sampling from other occupational groups and other years. The combined data supported this hypothesis. Other possible occupational and social class factors in coronary heart disease were considered, including psychologic and nutritional influences.

MAXWELL

Schnur, S.: Mortality Rates in Acute Myocardial Infarction. I. The "Normal" Yearly Variation, and the Effect of Hospital Admission Policy. Ann Int. Med. **39:** 1014 (Nov.), 1953.

The yearly mortality rate from acute myocardial infarction in four hospitals in a single community during the decade 1941–1950 was determined. A wide variation of rates from year to year in each hospital was noted, but the average rate for the decade appeared to be determined in large measure by the hospital's criteria and policy for admission and the type of patients treated. Conclusions concerning the effectiveness of a new drug or procedure drawn solely from finding a decreased mortality rate one year as compared with previous years, must be viewed with suspicion because of the wide "normal" fluctuation of rates from year to year due to the chance variation of small samples and the constantly changing proportion of seriously ill patients admitted. The hospital mortality rate cannot be used as a gauge of the professional abilities of the attending staff, nor can the rates of different hospitals be used to compare competence in the treatment of this disease because of the difference in severity of illness of patients admitted to various hospitals.

WENDKOS

Kurland, G. S., Schneckloth, R. E., and Freedberg, A. S.: The Heart in I^{131}-Induced Myxedema. Comparison of the Roentgenographic and Electrocardiographic Findings Before and After the Induction of Myxedema. New England J. Med. **249:** 215 (Aug. 6), 1953.

This study is concerned with the radiographic and electrocardiographic changes recorded in cardiac patients who were euthyroid prior to the induction of persistent hypothyroidism by one or more doses of I^{131}. The duration of the hypometabolism ranged from 2 to 53 months and averaged 27 months. Changes in size and configuration of the heart were studied in 27 patients and variations in the electrocardiograms were studied in 28 patients. Ten of 13 patients who showed good or striking improvement in angina pectoris from I^{131} treatment, showed no increase in the cardiac size. Two others had no increase during periods of 26 and 38 months of relief but later showed cardiac enlargement during exacerbations of angina pectoris and congestive heart failure. Five of 6 patients with angina pectoris unimproved by I^{131} treatment showed progressive increase in the size of the heart. Six patients with chronic congestive heart failure showed no cardiac enlargement during most of the 19 to 53 months of hypometabolism. Two patients with both angina pectoris and congestive heart failure showed marked

benefit from I^{131} therapy even though there was a marked, progressive increase in the size of the heart. The development of myxedema was associated with electrocardiographic changes which included decrease in voltage, flattening or inversion of the T waves and slight decrease in the Q-T interval. Treatment with thyroid produced reversion of these changes, and there was no further progression despite continued hypometabolism. These studies are felt to suggest that "myxedema heart," in the sense of a condition characterized by angina pectoris or congestive failure and marked electrocardiographic and radiographic changes, does not occur in patients with prolonged, controlled I^{131}-induced hypothyroidism.

ROSENBAUM

Marfori-Savini, L., Vulterini, S., Magalini, S. and Coltorti, M.: The Serum Lipoproteins (by Salting out with Sodium Sulphate) in Subjects Suffering from Coronary Atherosclerosis. Acta. med. scandinav. **146:** 148 (Fasc. 2), 1953.

This study is concerned with observations of the relation between cholesterol and proteins as determined by the distribution of serum cholesterol in the serum protein fractions obtained by sodium sulfate precipitation. Globulin fractions of the serum were precipitated by sodium sulfate at final concentrations of 15 per cent, 19 per cent, and 26 per cent. Patients with coronary atherosclerosis were found to differ from normal individuals in that the amount of protein in the albumin fraction was significantly lower, and there was a significant increase in the total globulin fraction and the 26 per cent globulin fraction. The albumin-linked cholesterol appeared lower in patients with coronary atherosclerosis, but there was no significant change in the cholesterol bound to other serum protein fractions. Furthermore, the cholesterol bound to the albumin fraction was influenced by the presence of coronary atherosclerosis, independent of the levels of albumin and cholesterol in the serum. The total serum cholesterol appeared to have a significant influence on the cholesterol of the albumin, total globulin and 15 per cent globulin fractions. The higher the serum total cholesterol, the higher is the cholesterol bound to the total globulin fraction. The cholesterol of the 15 per cent globulin fraction is higher in hypercholesteremic individuals.

These workers mention that, in the pathogenesis of atherosclerosis, the relations between proteins and cholesterol may be of greater importance from the point of view of the solution instability of the serum cholesterol, than of the absolute cholesteremia.

ROSENBAUM

Keyes, J. W., Drake, E. H., James, T. N., and Smith, F. J.: Survival Rates after Myocardial Infarctions with and without Long Term Anticoagulant Therapy. Am. J. M. Sc. **226:** 607 (Dec.), 1953.

Two groups of patients with myocardial infarction were compared for survival rates over periods of one or two years. The first group consisted of control patients receiving no anticoagulant therapy; the second group received treatment with Dicumarol on a long-term outpatient basis. Of the control group, 24.5 per cent of 106 cases with a single infarct died compared with 4.8 per cent of 21 treated cases in the first year. The data for those with recurrent infarcts were equally impressive; 31.7 per cent of the control group died compared with 13.0 per cent of the treated group. Five patients receiving long-term Dicumarol therapy developed new myocardial infarcts; four of these had been given transfusions because of hemorrhagic complications and died following recurrent infarction. The authors conclude that long-term anticoagulant therapy improves the prognosis of patients with either single or recurrent myocardial infarctions over a two-year period. Such therapy is hazardous in some instances and should not be attempted unless the risks are carefully weighed against the possible benefits.

SHUMAN

Trinidad, S., Grayzel, D. M., Rapoport, P., and Lee, N.: Aneurysm of the Coronary Artery. Ann. Int. Med. **39:** 1117 (Nov.), 1953.

A case is presented of aneurysm of the left circumflex coronary artery with an accompanying aortic aneurysm, bringing the total to 49 cases of true coronary aneurysms reported up to this date. This case is being classified under the category of the arteriosclerotic type, but it is likely that injury to the adventitia by hemorrhage or some form of arteritis was also responsible. Antemortem diagnosis is practically impossible. Coronary thrombosis, as in the case described in this report, is the frequent cause of death in patients with aneurysm of the coronary artery.

WENDKOS

Mason, R. E.: Clinical Diagnosis of Atherosclerosis of the Coronary Arteries. J. Am. Geriatrics Soc. **1:** 749 (Nov.), 1953.

Angina, infarction, abnormality of electrical activity and congestive failure are clinical manifestations of coronary atherosclerosis. There are a number of laboratory procedures which have been reported to be of help in the diagnosis of coronary atherosclerosis. Two procedures which are of great value when they give positive results are the electrocardiogram and the x-ray examination. The electrocardiogram may be diagnostic of coronary insufficiency when the record is taken during a spontaneous episode of angina pectoris, or when myocardial anoxia is brought about by one of the several types of stress tests. These tests may fail to give positive results in 50 per cent of patients with known coronary atherosclerosis and may give

falsely positive results in 22 per cent of perfectly healthy normal controls. If the criteria for positive findings are made more stringent so as to eliminate positive results in the normal controls, many diagnoses of coronary disease are likewise eliminated. Such stress tests, therefore, give far from the clear-cut results claimed by some authors though they may be diagnostic in some cases when strictly evaluated. X-ray examination gives evidence of coronary atherosclerosis in some patients. The coronary arteries may rarely be seen to contain calcium. More commonly, fluoroscopy or roentgenkymography may demonstrate a ventricular aneurysm following myocardial infarction. Ballistocardiography has yet to be established as a valuable clinical tool.

There is a group of laboratory tests which may be classified as having little or no value, per se, as applied to an individual patient for the purpose under discussion. This group includes detection of the various lipoprotein fractions of the serum by ultracentrifugation or by electrophoresis determination of the serum cholesterol level, the cholesterol-phospholipid ratio, the cholesterol-uric acid phospholipid index, somatotyping, and the flicker fusion test. By combining these procedures, it is possible to reduce partially the degree of error. These tests have been devised for the purpose of detecting atherosclerosis in general and are not only far from reliable in this respect, but give no information in regard to the state of the coronary arteries.

The authors concluded that thus far, no test has been developed which is diagnostic of coronary atherosclerosis in the majority of cases. It is only by the combined process of taking a detailed history without asking leading questions, performing an adequate physical examination and then applying certain of the tests which have been discussed, that even reasonable accuracy of diagnosis can be attained.

BERNSTEIN

ELECTROCARDIOGRAPHY

Folli, G., and Libretti, A.: Alternation of Left and Right Bundle Branch Block. Acta cardiol. **8:** 627 (Fasc. 6), 1953.

A case of a hypertensive patient is reported in whom, in the course of a bronchopneumonic infection, a pre-existent left bundle-branch block pattern transiently changed to a right bundle-branch block pattern. This is explained on the assumption that the intraventricular block was not in the bundle branches but in the free ventricular walls and caused by ventricular strain. The pulmonary infection caused a transient drop of blood pressure and relieved the left ventricular strain, and at the same time caused an increased load on the myocardium of the right ventricle.

PICK

Hoel, J., and Berg, A. H.: Persistent Diphtheritic Heart Disorders. A Follow-up Investigation. Acta med. scandinav. **145:** 393 (Fasc. 6), 1953.

In the years 1942–1946 a major epidemic had occurred with a total of 1,477 cases of diphtheria treated at the Kristiansand Hospital. Of these, 263 had clinical or electrocardiographic evidence of heart disease, and 26 of this group had died. This report is concerned with a follow-up study made in 1950–51 of the remaining 237 patients. Of this total 162 were re-examined by these observers, 48 answered questionnaires and 27 were lost. Of the 162 patients who were re-examined there was no instance of congestive heart failure, one patient had varying degrees of heart block with some episodes suggesting Stokes-Adams attacks, six patients had prolongation of the P-R interval, four showed bundle-branch block and six had depression of the S-T segments or changes in the T waves in leads I and II. Two patients showed cardiac enlargement, possibly of diphtheritic origin. Of the female patients, 25 bore children after the diphtheria with no cardiac complications even though three of them had some persistent electrocardiographic abnormalities.

ROSENBAUM

Koehler, E., and Spang, K.: The Ventricular Gradient in Myocardial Infarction. Arch. Kreislaufforsch. **20:** 138 (Dec.), 1953.

In 156 three-lead electrocardiograms on 75 patients with myocardial infarction, the frontal vectors of QRS and T areas and the ventricular gradient were determined and tabulated. In anterior wall infarction, the direction of $\hat{A}QRS$ is very variable and maximal deviations to the right or to the left are found in the presence of a ventricular aneurysm. The magnitude of $\hat{A}QRS$ decreases in the course of myocardial infarction and more so in anterior than in posterior infarction. It increases again in most cases during the period of restitution but never reaches pre-infarction values. $\hat{A}T$ rotates to the right in anterior, and to the left in posterior wall infarction, increases in magnitude at the height of infarction and usually does not return to its original position and magnitude. The direction and magnitude of the ventricular gradient are altered more by anterior than by posterior infarction. In the former it is displaced to the right, in the latter somewhat to the left. It may retain its normal position but is invariably reduced in magnitude. In all stages of myocardial infarction, cases may be encountered with normal angle of $\hat{A}QRS$ and $\hat{A}T$, or $\hat{A}QRS$ and $\hat{G}$. In the stage of maximal T alteration, $\hat{A}T$ is 10 degrees to the right of $\hat{A}QRS$ in most instances of anterior wall infarcts, and more than 60 degrees to the left of $\hat{A}QRS$ in about half of the cases with posterior wall infarct.

The direction of inhomogenous repolarization and the construction of the anomalous component

cording to Cabrera and Sodi Palleres is *exemplified* in several diagrams for anterior as well as for posterior wall infarcts.

PICK

Drewes, J., Effert, S., and Loogen F.: Electrocardiographic Observations in Heart Surgery. I. Transauricular Valve Fracture in Mitral Stenosis. Arch. Kreislaufforsch. **20:** 62 (Dec.), 1953.

The authors report electrocardiographic studies during and following mitral surgery in 24 patients. Premedication, anesthesia and opening of the chest and the pleura did not produce significant alterations of rhythm or contour. Instillation of Novocain into the pericardium was in the majority of cases followed by S-T deviations and increase in the amplitude of the P waves. Opening of the pericardium and manipulation of the left auricular appendage almost invariably produced numerous supraventricular premature beats. Introduction of the finger into the atrium was followed by runs of supraventricular tachycardia, and temporary occlusion of the mitral ostium during the procedure of fracturing by periods of ventricular tachycardia or of idioventricular rhythm. In addition, the following observations were made (these are independent of the stage of the operation): frequently complete or incomplete A-V dissociation, and occasionally transient ventricular flutter; or a monophasic deformation of the ventricular complex. The commonest finding following surgery is the development of electrocardiographic patterns characteristic of successive stages of pericarditis. In occasional instances auricular fibrillation or flutter occurred subsequent to surgery.

The practical importance of continuous recordings during mitral surgery lies in the possibility of recognizing in time serious disturbances of rhythm and contour, particularly during the time of intracardiac manipulations. In the evaluation of a postoperative electrocardiogram the common occurrence of a benign pericarditis must be taken into account.

PICK

Segers, M.: Notes on the Electrical Position of the Heart. Arch. mal. coeur **46:** 1091 (Dec.), 1953.

The author presents examples of intermittent complete and incomplete intraventricular blocks recorded simultaneously in the three aV limb leads and in V_6. With disappearance of beats of prolonged QRS duration, the direction of QRS changed independently in aV_L or in V_6. Thus, a pattern originally corresponding to an electrically horizontal position suddenly was converted to one indicating a vertical position, and vice versa. Since it is impossible that the electrical position of the same heart could vary from beat to beat, the author suggests that Wilson's concepts of "electrical position" and his terminology be abandoned. Einthoven's original terminology is to be preferred for analysis and description of the QRS direction in various leads of the frontal plane.

PICK

Osher, H. L., and Wolf, L.: Electrocardiographic Pattern Simulating Acute Myocardial Injury. Am. J. M. Sc. **226:** 541 (Nov.), 1953.

Abnormal displacement of the S-T segment encountered in myocardial injury consists of an elevation and upward bowing of the S-T segment and a symmetric T-wave inversion in leads facing the affected area. The authors describe such a pattern occurring in a patient without clinical evidence of any acute myocardial process. In the electrocardiograms obtained, the QRS interval is slightly prolonged with a configuration of right bundle-branch block, the R′ deflections merge with the S-T-T complex in a smooth, coved line, and the T waves are inverted over the right precordium. This pattern, occurring in normals, may represent an overlapping of ventricular depolarization and initial repolarizing potentials with fusion of the terminal portion of the QRS complex with the initial portion of the S-T-T complex. No changes in the serum potassium were found to account for this alteration.

SHUMAN

Holzmann, M., and Ramer, Z.: Contribution to the Knowledge of Electrocardiographic Alterations in Pulmonary Embolism. Arch. Kreislaufforsch. **20:** 117 (Dec.), 1953.

Case histories of three cases of acute cor pulmonale with unusual clinical manifestations and electrocardiograms are presented. In the first case, an instance of recurrent thrombophlebitis of leg veins, the clinical picture was dominated by typical anginal pain on effort, and the electrocardiogram showed two episodes of isolated T inversion in the precordial leads which could be mistaken for an atypical anterior wall infarct. The second case, in whom a pulmonary embolus occurred after surgery, likewise showed only T-wave inversion in the right precordial leads, accentuated and broadened by superposition of a large inverted U wave. In the third case the electrocardiogram showed classic features of recent posterior wall infarction with A-V block, except for negative T-waves in the right precordial leads. At autopsy massive pulmonary embolization was found but there was no trace of coronary disease.

These three selected cases demonstrate that exceptions may occur in the typical electrocardiographic pattern of acute cor pulmonale as established by MacGinn and White. It would appear that inversion of the T wave over the right precordium is the most consistent alteration suggesting the presence of acute cor pulmonale.

PICK

Remington, J. W., and Huggins, R. A.: Relation of Left Ventricular Ejection Period to the Q-T Interval of the Electrocardiogram. Am. J. Physiol. **175:** 185 (Nov.), 1953.

The end of the T wave and the end of ejection were apparently unrelated in these experiments. It was possible for the ejection period to change with fluctuating circulatory conditions without influencing electrocardiographic timing. The ascending aorta was occluded in order to prevent most of the ejection. Under these circumstances, the period of tension rise remained constant although conditions were varied and there was some change with cycle length. Peak tensions and the height of the T wave were almost simultaneous. Although the obstruction was released late in a cycle, ejection could start and last during most of the period of declining tension.

OPPENHEIMER

Van Dooren, F., and Boyadjian, N.: Prolonged QRS Complexes in Auriculo-Ventricular Dissociation. Acta cardiol. **8:** 608 (Fasc. 6), 1953.

The authors studied the contour of ventricular complexes in 43 cases with A-V dissociation caused by advanced A-V block. In 78 per cent the QRS was abnormally widened, and in 22 per cent it had normal contour. The predominant etiologic factor in the former group was arteriosclerotic heart disease.

In the interpretation of prolonged QRS complexes occurring in A-V dissociation, two possibilities must be considered, namely origin of the impulse activating the ventricles below the bifurcation of the common A-V bundle, or a supraventricular pacemaker associated with a ventricular conduction defect. The authors favor the latter explanation on the basis of the frequent finding of patterns of bilateral bundle-branch block, variations in the duration and shape of the QRS, persistence of QRS prolongation after restitution of A-V conduction, and on the basis of clinical facts.

PICK

Segers, M.: Preponderance in Precordial Leads. Acta cardiol. **8:** 602 (Fasc. 6), 1953.

The author presents further examples of clinical electrocardiograms in support of his previously published concept implying a common genesis of preponderance curves and patterns of incomplete and complete bundle-branch block. In cases of intermittent bundle-branch block and instances of aberrant ventricular conduction of auricular premature systoles, gradual transitions were observed of patterns of ventricular preponderance into frank bundle-branch block patterns. In simultaneously recorded multiple leads, the bundle-branch block can be seen over the precordium, while corresponding beats in the limb leads show little or no abnormality. Such a combination is considered by the author as a particular type of "incomplete intraventricular block."

PICK

Segers, M., and Hendricks, J.: Electrokymographic Exploration in a Case of Intermittent W.P.W. Syndrome. Acta cardiol. **8:** 643 (Fasc. 6), 1953.

In a young woman without clinical evidence of heart disease but with a Wolff-Parkinson-White syndrome of type B (pre-excitation of the right ventricle) electrokymograms were recorded simultaneously with electrocardiograms during periods of alternation of normal and anomalous ventricular activation. While there was no difference in the two types of beats in the aortic electrokymogram, curves obtained from the pulmonary artery showed distinct alternation with a 25 to 30 per cent reduction in the amplitude of the anomalous beats. The beginning of ventricular ejection measured as distance from the beginning of the P wave to the beginning of the electrokymographic deflections was the same in both types of beats. It is concluded that anomalous ventricular activation by pre-excitation changes the mechanical effects of ventricular contraction without affecting the duration of contraction.

PICK

Contro, S.: The Diagnosis of Atrial Flutter by Means of Graphic Methods. Cuore e circolaz. **37:** 1, 1953.

Nine cases of auricular flutter are presented. In all of them the electrocardiogram in the limb leads, unipolar limb leads, and precordial leads was recorded, as well as the phonocardiogram. The jugular tracing was also recorded in five cases; the electrokymograms of the atria were recorded in four.

The atrial waves were particularly apparent in leads III and aV_F in some cases, in V_1 and V_2 in others. The phonocardiogram gave a good registration of atrial tones in some of the cases. In two cases out of five, the jugular tracing showed high atrial waves in diastole. The electrokymogram demonstrated rapid and regular atrial waves of the atrial borders in the four cases where it was recorded. The author advocates the use of mechanical or roentgenologic graphic tracings in doubtful cases.

LUISADA

Guidotti Mori, P., and Pala, A.: The Electrocardiographic Diagnosis of Coronary Insufficiency by Means of the So-called "Left Intracavitary Lead." Cuore e Circolaz. **37:** 224, 1953.

Odlc and co-workers described a unipolar lead based on the recording of left supraclavicular potentials by means of an exploring electrode. This lead should record left ventricular cavity potentials. This lead was studied by the authors in 121 subjects together with the convention leads. No special superiority of this lead over aV_R was found and no diagnostic advantage was recognized by the authors.

LUISADA

Smith, J. E.: Comparison of the Displacement, Velocity, and Acceleration Ballistocardiograph in Coronary Heart Disease. Am. Heart J. **46:** 692 (Nov.) 1953.

Simultaneous calibrated recordings of displacement, velocity, and acceleration components of body motion were taken on 50 normal adults and 20 cases of proved coronary heart disease between the ages of 30 and 40 years. Displacement and velocity standards are based on absolute measurements of the I-J segment. Also, the rates of H-I, I-J, and J K segments are expressed as a percentage relationship to each other. Acceleration standards are based on measurement of the aJK segment and from the base line to the aK peak. The demonstration of abnormality of form and amplitude in coronary type heart disease is more pronounced and more definitive in pattern on the acceleration curves than in either the displacement or velocity.

RINZLER

von Wittern, W.: Ballistocardiography with Elimination of the Influence of the Vibration Properties of the Body. Am. Heart J. **46:** 705 (Nov.), 1953.

This report deals with the technical aspects of a ballistocardiograph which is designed to eliminate the influence of the vibration properties of the body. The importance of this system is discussed, pertinent mathematical formulas are given, and typical records taken with this new instrument are illustrated.

RINZLER

ENDOCRINE EFFECTS ON CIRCULATION

Liddle, G. W., Bennett, L. L., and Forsham, P. H.: The Prevention of ACTH-Induced Sodium Retention by the Use of Potassium Salts: A Quantitative Study. J. Clin. Investigation **32:** 1197 (Dec.), 1953.

Sodium retention may be produced by the administration of large doses of corticotropin or adrenal steroids. With this adrenal therapy, there is an increased excretion of potassium and it is common practice to supplement the diets of patients receiving these hormones with potassium salts. Administration of potassium has been found to be effective in overcoming sodium retention. Therefore, a study was carried out on 14 subjects with miscellaneous diseases who received corticotropin or cortisone.

It was found that potassium salts tended to reverse many of the effects of adrenal steroids on electrolyte metabolism. Large doses of potassium chloride or potassium acetate resulted in a diuresis of sodium, particularly in those receiving corticotropin or cortisone. Proportionately, more sodium was excreted than chloride. A decrease in urinary phosphate, ammonia, and titratable acid, and an increase in urinary bicarbonate and chloride, were also noted.

The authors conclude that sodium retention due to cortisone or corticotropin therapy can be prevented by the daily administration of 200 mEq. or more of potassium.

WAIFE

HYPERTENSION

Levin, E. B.: Pheochromocytoma before and after Surgery. Arch. Int. Med. **92:** 906 (Dec.), 1953.

A case of pheochromocytoma, studied before and after surgery, is reported. Special attention is given to the laboratory findings, pharmacologic tests, and roentgenographic diagnostic procedures. The literature on pheochromocytomas is reviewed regarding the effect of epinephrine on the adrenal-pituitary axis. This review and the findings in this case lead the author to conclude that chronic epinephremia does not produce adrenal cortex changes. The metabolic effects of epinephrine are discussed. The clinical pictures of thyrotoxicosis and diabetes in cases of pheochromocytoma are noted. The relationship of these symptoms and findings to pheochromocytoma are analyzed.

BERNSTEIN

Geschicter, C. F., and Popovici, A.: Phrenic or Postemphysematous Hypertension. Arch. Int. Med. **92:** 767 (Dec.), 1953.

In a study of 60 patients over the age of 40 with emphysema and bronchial asthma of two or more years' duration, all had some degree of arterial hypertension. Using similar standards for the upper limits of normal blood pressure (160/90 mm. Hg), the corresponding percentage of persons with hypertension in the general population is between 20 and 25 per cent. In a series of 15 patients with extrinsic emphysema not complicated by asthma but resulting from such factors as fixation of the chest wall from spondylitis, senility, and osteoarthritis, hypertension also occurred, particularly in cases complicated by pulmonary fibrosis or by lordosis in association with abdominal obesity.

It is concluded that long-standing emphysema with loss of negative intrathoracic pressure in patients over 40 can lead to hypertension, particularly when the emphysema is complicated by bronchial asthma or pulmonary fibrosis, or when it exists in combination with postural lordosis accompanied by obesity. Phrenic hypertension appears to be the result of loss of intrapleural negative pressure, with increased venous pressure associated with renal congestion and compensatory arteriolar spasm.

Twenty-one of 60 patients with asthma and emphysema showed some degree of myocardial damage in the electrocardiogram. Fourteen of 25 patients with myocardial damage had both emphysema and hypertension. Seven out of 35 patients without hypertension, but with emphysema, had myocardial damage. The authors believe that the mechanism of hypertension in these cases is im-

paired venous coronary return to the right auricle in the presence of increased intrapleural pressure.

BERNSTEIN

Saracoglu, K.: The "Crossed Test" and Other Tests for Hypertension. Acta. med. scandinav. **144:** 473 (Fasc. 6), 1953.

The author describes a pressor test for hypertension which is said to give results similar to those of the cold-pressor test of Hines and Brown. This new pressor test consists of the intravenous injection of 10 cc. of 30 per cent hypertonic saline solution and the rise in pressure is observed in three to five minutes. A depressor test consisting of the intravenous injection of 10 cc. of 10 per cent solution of sodium bromide is also described. The blood pressure is said to fall after two to five minutes and reaches its lowest level after 15 to 30 minutes, remaining depressed for 1 to 24 hours. This depressor test is said to be more effective than any other available. These tests are positive if the hypertension is neurogenic; they are said to be positive in early essential hypertension and in acute nephritic hypertension, which, in the author's opinion, has a neurogenic origin. The tests are negative in chronic nephritis and in the advanced stages of all forms of hypertension.

The "crossed test" consists of the initial injection of 10 cc. of 10 per cent solution of sodium bromide followed in two minutes by the cold-pressor test or the hypertonic saline pressor test. The response to the pressor test is said to be negative if essential hypertension is present because the sympathetic pathways have been blocked by the sodium bromide.

The author reports briefly upon the treatment of essential hypertension with daily intravenous injections of 10 cc. of 10 per cent solution of sodium bromide for a period of 10 days. The treatment may be repeated after an interval of 10 days. Both objective and subjective benefit is said to result in cases of essential hypertension, with less satisfactory results in malignant hypertension.

ROSENBAUM

Seligman, A. W., Ferguson, F. C., Garb, S., Gluck, J. L., Halpern, S. L., and Goodgold, M.: Evaluation of Treatment in Hypertension: Effects of Cinchona Alkaloids. Am. J. M. Sc. **226:** 636 (Dec.), 1953.

The "double-blind" procedure was employed to compare the effects of quinidine and quinine with those of a placebo upon hypertension in 44 patients. Quinidine produced rather striking effects on the blood pressure and symptomatology of hypertensive disease. However, these effects were duplicated in the group receiving the lactose placebo. The statistical analysis of the data reveals that the results are not significantly different from chance distribution. Similarly, quinine was shown to be without specific effects. It is of interest to note that in this study it was possible to improve the symptoms in patients with "fixed" hypertension; that the subjective opinions of patients and doctors are valueless in evaluation of therapy; and that statistical analysis alone is not an adequate control of the experiment. It is considered that the "double-blind" method should be an integral part of any study on hypertension.

SHUMAN

Merrill, D. H., and Kenyon, K.: 1-Hydrazinophthalazine (Apresoline) in the Treatment of Hypertensive Disease: A Clinical Trial with a Control Group. Am. J. M. Sc. **226:** 623 (Dec.), 1953.

The effect of Apresoline in the treatment of hypertension was evaluated by administering the drug to 37 patients in appropriate dosage from 100 to 800 mg. daily. A control group of 28 patients was given a placebo, identical in appearance to the drug for comparable periods. Of the treated group, 12 had a drop of 20 per cent or more either while supine or sitting. One of the control subjects had a similar decline of blood pressure. Severe side effects necessitated discontinuance of Apresoline in 11 instances; these consisted of headache, vomiting, fever or tachycardia. Headache occurred to some extent in nearly every patient receiving the drug. Two patients discontinued the placebo because of headache and nausea. Three hospitalized patients with uremia were adversely affected by the drug so that its use in uremia is contraindicated. It is concluded that Apresoline may be of value in the treatment of hypertension but that its effects are not predictable in individual cases.

SHUMAN

McCubbin, J. W., and Page, I. H.: Modification of the Hypotensive Action of 1-Hydrazinophthalazine (Apresoline) by Priscoline, Hexamethonium and Section of the Carotid Sinus and Aortic Buffer Nerves in Normal and Renal Hypertensive Dogs. Am. J. M. Sci. **226:** 632 (Dec.), 1953.

The hypotensive effect of intravenous Apresoline is either unchanged or diminished by prior treatment with hexamethonium; this effect was increased by prior treatment by Priscoline in normal and renal hypertensive dogs. The combined effect of Apresoline and Priscoline appears to represent a synergistic action in lowering the blood pressure. The sensitivity of dogs with renal hypertension to Apresoline was not increased while that of neurogenic hypertensive dogs was increased. Section of the carotid sinus nerves did not produce hypertension or tachycardia but did enhance the hypotensive action of Apresoline. The results suggest that combined therapy with Priscoline and Apresoline would be more effective in the treatment of

hypertension than either drug alone or with hexamethonium.

SHUMAN

Mills, L. C., Moyer, J. H., and Skelton, J. M.: The Effect of Norepinephrine and Epinephrine on Renal Hemodynamics. Am. J. M. Sc. **226:** 653 (Dec.), 1953.

Renal clearance tests were performed on a group of normotensive subjects and on hypertensive patients receiving hexamethonium before and after the infusion of norepinephrine and epinephrine. Norepinephrine produced a depression of renal plasma flow but had little effect on glomerular filtration rates. Renal vascular resistance and the filtration fraction were elevated by the drugs. The tubular transport of para-aminohippurate was not affected by either agent. The hemodynamic changes were attributed to an increase in both afferent and efferent arteriolar resistance. There is no evidence of a decrease in the number of functioning nephrons as has been observed previously in dogs. In patients whose renal function was depressed by hexamethonium, there was a return of glomerular filtration rate toward control values. This observation suggests that in the treatment of hypotensive states, the elevation of blood pressure may overbalance the renal vasoconstrictor effect so that renal function will be improved.

SHUMAN

Mendlowitz, M.: The Treatment of Hypertension with Drugs. Ann. Int. Med. **39:** 999 (Nov.), 1953.

The treatment of hypertension should be undertaken only when that disease, under observation, represents a hazard to a patient's life or health. Drug therapy is usually directed at the neurogenic factor. A variety of drugs is available for blocking the motor synapses and nerve endings concerned in the excessive sympathetic nerve discharge believed to be a factor in hypertension. For the best results, this should be defined by testing procedures in advance of and during treatment. The limiting factors are usually tolerance and side actions. At the cortical level, barbiturates are the most useful drugs, although these may be replaced eventually by Rauwolfia serpentina. At the hypothalamic level, 1-hydrazinophthalazine and protoveratrine are the most effective, whereas at the ganglionic level, hexamethonium bromide or chloride is the drug of choice. Parenteral administration of this drug is preferred to oral administration because of the inherent serious dangers of the latter. A block of sympathetic nerve endings, smooth muscle or of capillaries is, at present, of minimal practical value in the treatment of hypertension. Salt depletion by diet and dietary adjuvants appears to affect the non-neurogenic or intrinsic factors in hypertension. Sympathectomy should be reserved for patients with a large neurogenic element who fail to respond to adequate medical therapy. In many cases, judiciously combined treatment provides the most satisfactory results.

WENDKOS

Hood, B., Björk, S., Angervall, G., and Rudbäck, H.: Muscular Exercise in Essential Hypertension. The Effect of Hexamethonium Chloride (C6). Acta med. scandinav. **147:** 213 (Fasc. 3), 1953.

Observations were made of the blood pressure responses during and following muscular work in a series of patients with malignant and severe benign essential hypertension before and during treatment with hexamethonium chloride (C6). It was found that the blood pressure did not reach as high a level during bicycling when the patient was receiving hexamethonium in the usual clinical dosage. Furthermore, under the influence of the drug there was a considerable, prolonged fall in the blood pressure when the patient was in the sitting position after work. These responses to hexamethonium were just as marked in patients who had received the drug for three months as in patients started on it more recently. Under the influence of hexamethonium the pulse rate rise in response to exercise was lower, there was no tendency to progressive increase during the work period, and the return to normal was more prompt. After passive standing, patients receiving hexamethonium over long periods were found to show a definite "overshoot" in the blood pressure upon resuming the horizontal position.

ROSENBAUM

Pascoe, S. C., and Evans, J. M.: Urethral Apoplexy; An Early Symptom of Malignant Hypertension. Am. J. M. Sc. **226:** 533 (Nov.), 1953.

Urethral bleeding was found to be an initial symptom in four patients with malignant hypertension. In two instances the site of bleeding was localized in the anterior urethra. Hemorrhage was observed in association with renal insufficiency as manifested by nitrogen retention in each instance. Thus, renal insufficiency was thought to be a factor in urethral bleeding seen in these hypertensive subjects.

SHUMAN

PATHOLOGIC PHYSIOLOGY

Blumberger, K. J.: Studies on the Dynamics of Pulsus Alternans. Arch. Kreislaufforsch. **20:** 25 (Dec.), 1953.

The author recorded in four cases of pulsus alternans the electrocardiogram, the phonocardiogram, and the carotid pulse curve and determined the following values: the time of isometric contraction, the ventricular ejection time, the duration of the anacrotis of the pulse curve, and the interval between the Q wave of the electrocardiogram and the beginning of the pulse curve ("transformation time").

In pulsus alternans the smaller systoles have a longer time of isometric contraction, an anacrotic elevation of longer duration, and a shorter ejection time when compared with the larger systoles. Both types of contractions, however, differ from those seen in normal cardiodynamics in that the mechanical systole starts with a certain delay (prolonged time of ventricular transformation).

These findings were compared with those present in other conditions in which differences of systolic strength are associated with irregular heart action e.g. premature beats (pseudoalternans) or in auricular fibrillation. Under such circumstances the duration of the anacrotis depends on the presystolic pressure gradient between the ventricles and the aorta, while the onset of the isometric phase is related primarily to ventricular filling. Thus, true alternans and pseudoalternans differ not only in their genesis but also in their dynamics.

None of the studied cases had an electrical alternans but all had an abnormally large heart and contour alterations of the electrocardiogram indicating myocardial pathology of some degree.

The author concludes that the cause of pulsus alternans is severe damage of the ventricular myocardium with impairment of its contractility. Partial asystole, as postulated by Gaskell and Wiggers appears unlikely in human pathology and "has at the present no more significance than that of a working hypothesis."

PICK

Yu, P. N. G., Lovejoy, F. W. Jr., Joos, H. A., Nye, R. E. Jr., and Simpson, J. H.: An Unusual Case of Massive Pericardial Effusion with Hemodynamic Studies. Ann. Int. Med. **39:** 928 (Oct.), 1953.

This report describes the case of a 70 year old patient who had massive pericardial effusion for at least 15 months preceding his hospital admission. Apart from increasing dyspnea and edema during this period, his deterioration was remarkably slow. This chronicity of symptoms suggested a benign process and accords with the failure to demonstrate a definite etiologic factor which included intensive search for evidence of tuberculous infection in the pericardial effusion removed by aspiration on several occasions, and in the pericardial exudate removed during a subsequent pericardiectomy. This operation was followed by remarkable clinical improvement. During the first pericardial aspiration, after removal of 150 cc. of pericardial fluid, although the gradient between the mean right atrial and intrapericardial pressures was 12 mm. Hg, the pressure gradient at the point of the expiratory pause was only 1 mm. Hg. These gradients increased to 16 and 5 mm. Hg, respectively, after 1,400 cc. of pericardial fluid were withdrawn. Before the second pericardial aspiration the low cardiac output (4.32 liters per minute) was manifested by the wide A-V oxygen difference, indicating increased extraction of oxygen by the tissues. In addition, with a relatively rapid heart rate, the stroke volume was low. There was a distinct elevation in the right atrial, superior vena caval and peripheral venous pressures. Immediately after the removal of 1,400 cc. of pericardial fluid, a definite decrease in the mean right atrial and superior vena caval pressures was observed, although both the cardiac output and stroke volume failed to show a significant change. These findings suggest that, in this case, aspiration of a considerable amount of pericardial fluid caused prompt reduction of the venous and right atrial pressures, whereas improvement in cardiac index was insignificant and increase in stroke index was delayed. Six months following pericardiectomy the patient's striking improvement was associated with little venous distention and almost normal mean right atrial pressure. However, the cardiac output at rest was unchanged. The stroke volume was definitely increased because of the slower heart rate. Thus, the patient was able to maintain the same cardiac output with a slightly elevated venous pressure and essentially normal heart rate, in contrast to the markedly increased venous and right atrial pressures and a relatively rapid heart rate before operation. The elevated pulmonary artery and "capillary" pressures observed during the postoperative cardiac catheterization reflect some impairment of the blood flow through the left side of the heart. There was no clinical evidence of mitral valvular disease, frank left ventricular failure or chronic pulmonary disease to account for this. It is quite likely that some interference with diastolic filling of the left ventricle existed, perhaps due to residual pericardial and/or myocardial scarring.

WENDKOS

Hilden, T.: The Effect of Tetraethylammonium Bromide (Etylon) on Cardiac Asthma and Acute Pulmonary Edema. Acta. med. scandinav. **147:** 175 (No. 2), 1953.

The author reviews his beliefs regarding the pathogenesis of paroxysmal nocturnal dyspnea. It is his opinion that there is an increased venous return in the recumbent position associated with a certain hydremia resulting from resorption of latent or manifest edema, which increases the underlying pulmonary congestion. This gives rise to reflex changes in the respiration, such as polypnea and bronchospasm, and in the circulation, such as a rise in the blood pressure and pulse rate. The increased blood pressure places an increased stress upon the left ventricle. Because a rise in blood pressure appears to be an important factor in cardiac asthma and acute pulmonary edema, the effect of Etylon (tetraethylammonium bromide) in these conditions was studied.

Etylon, a 10 per cent solution of tetraethylammonium bromide, was given slowly intravenously in doses of from 0.8 to 5.0 ml. to two patients with

cardiac asthma and five patients with acute pulmonary edema with hypertension. Two patients were benefited within two to three minutes, and three others were much improved within 5 to 10 minutes. Transitory collapse occurred in one patient, and another, who was severely ill, died soon after admission. The improvement resulting from the drug is attributed to acute relief of the left ventricle due to reduction in the systemic blood pressure. Reduction of a pathologically elevated venous pressure may be an additional factor. This drug is not without considerable risk, however, especially if the effect upon the blood pressure becomes very pronounced with resultant deficient coronary circulation. It is recommended that tetraethylammonium bromide be used in cardiac asthma and acute pulmonary edema only when the usual therapy fails and careful controlling observations of the blood pressure must be made.

ROSENBAUM

Wolter, H. H., Bayer, O., Loogen, F., and Rippert, A.: The So-Called Pulmonary Capillary Pressure Curve and its Relation to Pressure Curves of the Right and Left Atrium. Cardiologia **23:** 319 (Fasc. 6), 1953.

The dependence of pulmonary wedge pressure curves on the pressure in the atria was analyzed. In a number of patients left atrial pressure curves were obtained by passing the catheter through an interatrial communication, or by introducing it into the chamber during mitral surgery.

A remarkable resemblance was found between the pressure curve of either atrium and the "pulmonary capillary pressure" curve in various congenital lesions as well as in acquired mitral disease. On the basis of their observations, the authors came to the conclusion that pulmonary capillary pressure curves represent a "transmitted image" of pressure variations in the left atrium, and abnormalities of the atrial pressure are reproduced in the pulmonary wedge pressure curve. Systolic and diastolic distortions of such curves are described and illustrated, and their mode of origin and clinical significance are discussed. It is pointed out that such tracings make it possible to recognize mitral regurgitation even of mild degree, or if it is associated with mitral stenosis. Finally a method is described to determine the time of diastolic filling from capillary pressure curves, which gives more accurate results than measurements based on carotid pulse tracings.

PICK

Lequime, J., Courtoy, P., and Kenis, J.: Circulatory Dynamics in the Course of Constrictive Pericarditis. Acta cardiol. **8:** 621 (Fasc. 6), 1953.

The authors present hemodynamic studies in a typical case of constrictive pericarditis. Pulmonary arterial and capillary pressures were elevated, the cardiac output was low and failed to respond adequately to the increased metabolic demands during exercise. Thus, in every aspect, the findings corresponded to those found ordinarily in chronic left heart failure. In order to evaluate the role of the condition of the left ventricular myocardium in the production of the abnormal hemodynamics, cardiac output determinations were repeated 45 minutes after intravenous injection of 1 mg. digoxin. However, the resting and exercise data remained practically unchanged. The absence of any response to digitalis suggests that, at least in this case, the constrictive pericarditis, and not heart failure, was the cause of the abnormal hemodynamic behavior.

PICK

Uricchio, J. F., and Calenda, D. G.: The Failure of Hypertonic Saline in the Treatment of Hyponatremia and Edema in Congestive Heart Failure. Ann. Int. Med. **39:** 1288 (Dec.), 1953.

An evaluation of the treatment of hyponatremia and edema in congestive failure with hypertonic saline was made in seven cases. It was observed that this method of treatment is ineffective and may prove harmful. The period of fluid restriction during the course of the infusion of the hypertonic saline is unbearable for most patients, and the syndrome is invariably fatal.

WENDKOS

Törnblom, N.: Venoarterial Lipid Difference and Hyperlipemia. Acta. med. scandinav. **146:** 224 (Fasc. 3), 1953.

A patient with essential hyperlipemia was studied during two separate 24-hour periods. The lipid content of the venous serum always exceeded that of the arterial serum and the mean differences for the two periods were 97 mg. per cent and 145 mg. per cent. The lipid content of the venous and arterial serum was also studied in 35 obese patients and 9 healthy students. The lipid content of the venous serum was almost always higher than that of the arterial serum. When the lipid content of the venous serum was high, the venoarterial lipid difference was usually large. The same was true, to a lesser degree, when the lipid content of the arterial serum was high.

From these observations it is concluded that, during the passage of blood through one or more of the central body organs, there is a reverse change in the lipid difference in the blood. The author mentions the earlier work of Roger and Binet which demonstrated a higher lipid content of the blood in the right than in the left heart, and suggested that this reverse change might occur in the lungs.

ROSENBAUM

Webb, R. C. Jr., and Starzl, T. E.: The Effect of Blood Vessel Pulsations on Lymph Pressure in Large Lymphatics. Bull. Johns Hopkins Hosp. **93:** 401 (Dec.), 1953.

A study was made in dogs of rhythmic intralymphatic pressure changes in the thoracic duct.

Occlusion of the aorta demonstrated that the lymphatic pulse is transmitted from the arteries ("from contiguous large arteries," according to the suggestion of the authors). These transmitted pressure changes apparently keep the lymph in continual pulsatile motion which, because of the high degree of valve competence, is of necessity oriented toward the venous drainage sites.

McKusick

Björk, V. O.: Circulation through an Atelectatic Lung in Man. J. Thoracic Surg. **26:** 533 (Nov.) 1953.

The author described a method for determining the relative blood flow through each lung in man during intrathoracic operations. Applied to patients with total atelectasis or a destroyed lung, he noted that the oxygen saturation of blood in the aorta was the same before and after occlusion of the pulmonary veins from a diseased lung. The amount of circulation through such a structure during the operation was found to be, on an average, 98 ml. per minute. In cases of total atelectasis, only a negligible amount of blood passed through the pulmonary artery.

It was concluded that the local pulmonary circulation in the presence of chronic atelectasis or destroyed lung is markedly reduced.

Abramson

St. George, S., Naegele, C. F., French, F. S., Rosenman, R. H., and Friedman, M.: A Quantitative Study of the Digitoxin Content of Edema Fluids. J. Clin. Investigation **32:** 1222 (Dec.), 1953.

The content of digitoxin in the peritoneal, pleural, and subcutaneous edema fluids of patients with edema of cardiac and hepatic origin was determined by using the embryo duck heart microassay technic. No digitoxin was detected in specimens removed from four of eight digitalized patients; minute amounts were found in the other four specimens. The maximal content of digitoxin was 20 μg. per liter in the ascitic fluid of a patient with hepatic cirrhosis.

It is believed that the rapid diuresis of even large quantities of edema fluid would not lead to the hypothetic "redigitalization following rapid diuresis."

Waife

PATHOLOGY

Tseng, H. L., and Roulet, F.: Cardiac Involvement in Miliary Tuberculosis: Am. Rev. Tuberc., **68:** 771 (Nov.), 1953.

This case presented unquestionable miliary tuberculosis of the heart and, in addition, there was the unusual formation of thrombi in the small coronary arteries with necrosis of the surrounding myocardial fibers and inflammatory cellular reactions. The possibility of emboli coming from the thrombi of the uterine plexus can be excluded by the closed foramen ovale and the absence of emboli in the pulmonary vessels.

With the aid of special stains for elastic fibers and fibrin, the present writers found fibrinoid swelling of the media, disintegration of the intima with partial disappearance of the internal elastic membrane, and some proliferation of the endothelium. It is believed that there are pathologic changes in the vessels as described above, followed by formation of thrombi by the deposit of platelets, blood corpuscles, and tubercle bacilli in the same way that thrombi are formed in inflamed or injured vessels in other parts of the body. The thrombi gradually became larger and finally, complete occlusion of the lumen occurred, resulting in focal necrosis of myocardial fibers and inflammatory cellular reactions.

Bernstein

PHARMACOLOGY

Lutembacher, R.: The Motionless Heart. Arch. mal. coeur **46:** 1068 (Dec.), 1953.

According to the author, apparent immobility of the heart can be produced in animal experiments by several drugs acting on the heart muscle through different mechanisms.

(1) *Digitalis glycosides or calcium chloride (passive retraction.)* Toxic doses produce an increasing shortening of the muscle fibers with decreased power of relaxation; the amplitude of the systolic contractions as well as that of the diastolic relaxations decreases to the point at which the heart ceases to beat. It is said that the heart is arrested in systole, but actually there is a lack of diastole. At this time, no changes of electric potential can be detected. The author's explanation concerning the effect of these drugs is that they damage the "contractile substance" within the "elastic membranes." The muscle is biologically dead. If the drugs are applied in less toxic doses, the effect is reversible.

(2) *Acetylcholine and calcium chloride simultaneously or successively applied (active retraction).* The heart is arrested in systole, but changes of electric potential can be registered. The electrocardiogram shows ventricular fibrillation, extrasystoles, or "incomplete systoles" starting from the base and moving toward the apex. In these cases, the activity of the contractile substance persists but is masked by a "rigidity of the elastic membrane" caused by the action of the two drugs.

(3) *Cobalt.* The heart is arrested in diastole. Changes of electric potential can be detected only after mechanical irritation of the heart. Cobalt affects the elastic membranes by "paralyzing" them and inhibits the automaticity, while the biologic activity of the contractile substance is preserved.

(4) *Formol.* The effect is similar to that caused

by acetylcholine and calcium chloride, with the difference that the arrest may occur either in systole or in diastole.

The author makes no attempt to investigate the chemical nature of the contractile substance or of the membrane in order to explain the action of these drugs.

LUISADA

Sprague, H. B., and Tansey, W. A.: Fever as a Sign of Quinidine Toxicity. Report of Sensitivity in Two Brothers with Thyroid Disease. New England J. Med. **249:** 796 (Nov. 12), 1953.

The cases of two brothers (age 42 and 48 years) with mild hyperthyroidism and auricular fibrillation are described. Both developed drug fever (temperature of 104 to 105 F.) in association with quinidine therapy. Mild diarrhea was the only other toxic manifestation. Both had had quinidine for some time prior to the first evidence of toxicity or fever. Although fever is a rare manifestation of quinidine sensitivity, the development of fever in a patient receiving this medication should not be mistaken for cardiovascular or other complications.

SAGALL

Page, I. H., and McCubbin, J. W.: Cardiovascular Action of 1,1-Dimethyl-4-Phenylpiperazinium Iodide (DMPP). A Ganglion Stimulating Agent Useful in the Diagnosis of Pheochromocytoma. Am. J. Med. **15:** 675 (Nov.), 1953.

DMPP (1,1 dimethyl-4-phenylpiperazinium iodide), a potent sympathetic ganglion stimulating agent, proved useful in the diagnosis of pheochromocytoma in one patient because of its strong and specific action on ganglia and adrenal medullary tissue. It ensures a high secretory activity of the tumor, the effect of which is specifically inhibited by adrenergic blocking agents.

Extensive pharmacologic tests indicated that DMPP stimulated sympathetic ganglia more powerfully than nicotine and tetramethylammonium iodide and had less ganglion paralyzing action than nicotine in dogs, cats, rabbits and man. It differed from nicotine in that its vasopressor action was largely independent of carotid and aortic chemoreceptor function. Respiratory stimulation depended in part upon stimulation of these chemoreceptors. The pressor effect of DMPP depended upon release of epinephrine and/or norepinephrine from the adrenal glands and liver and stimulation of sympathetic ganglia with resultant vasoconstriction and cardioacceleration. Stimulation of parasympathetic ganglia caused initial transient bradycardia and fall in blood pressure that tended to inhibit the pressor action of DMPP. Tetraethylammonium chloride, nicotine and hexamethonium inhibited the ganglion-stimulating action of DMPP. The adrenergic blocking agents, Priscoline, Regitine, and RO 2-3248 inhibited the pressor action of DMPP to a degree directly dependent upon the inhibition of pressor response to norepinephrine. Response to DMPP was unaltered by production of chronic neurogenic hypertension in dogs by section of the carotid sinus and aortic depressor nerves.

HARRIS

McCall, M. L.: Cerebral Circulation and Metabolism in Toxemia of Pregnancy. Observations on the Effects of Veratrum Viride and Apresoline. Am. J. Obst. & Gynec. **66:** 1015 (Nov.), 1953.

The author reports upon the effect of the administration of Veratrum viride and Apresoline on the circulatory and metabolic functions of the brain in 24 patients with toxemia of pregnancy and 18 normal pregnant women. Quantitative measurements were obtained of cerebral blood flow, cerebral oxygen utilization, cerebral vascular resistance, arteriovenous oxygen difference and blood gases before and after administration of the drugs. Veratrum was found to significantly lower the increased cerebral vascular resistance and mean arterial blood pressure present in toxemia of pregnancy; the other measurements were not affected. Apresoline, in addition to lowering cerebral vascular resistance and arterial pressure, increased the cerebral blood flow and oxygen utilization by the brain.

SHUMAN

McCall, M. L., and Taylor, H. W.: The Action of Hydergine on the Circulation and Metabolism of the Brain in Toxemia of Pregnancy. Am. J. M. Sc. **226:** 537 (Nov.), 1953.

Cerebral vascular resistance is increased in toxemia of pregnancy as demonstrated in studies employing the nitrous oxide method of Kety and Schmidt for determining cerebral blood flow. The effect of Hydergine, a combination of three new ergot alkaloids, upon the circulation and metabolism of the brain in toxemia of pregnancy was studied by this procedure. Quantitative studies of cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance, mean arterial pressure, respiratory quotient and blood gases were made in both normal and toxemic pregnant women before and after Hydergine administration in doses of 0.6 mg. intramuscularly. Cerebral vascular resistance and mean blood pressures were significantly depressed in both groups. However, the other factors studied revealed no change after the administration of Hydergine. Thus hemostasis is maintained within the brain despite circulatory alterations elsewhere induced by the drug.

SHUMAN

Ricketts, C. R., Walton, K. W., vanLeuven, B. D., Birbeck, A., Brown, A., Kennedy, A. C., and Burt, C. C.: Therapeutic Trial of the Synthetic Heparin Analogue Dextran Sulphate. Lancet **6794:** 1004 (Nov. 14), 1953.

The naturally occurring anticoagulant, heparin, has certain disadvantages, notably the necessity for frequent parenteral administration, its expense, occasional sensitization reactions and variation in chemical composition of different batches. Accordingly, the synthetic heparin analogue, dextran sulfate, was tried clinically in 24 patients with embolic or thrombotic phenomena.

Dextran sulfate resembled heparin in being comparably safe and nontoxic, in being quick-acting, in losing its effect rapidly on withdrawal, and in its capacity for neutralization in emergency. It must also be administered parenterally, but its somewhat greater duration of anticoagulant effect allows its administration at longer intervals. The control of therapy requires no more elaborate investigation than estimation of the clotting-time before each injection. The relative ease of its manufacture should allow cheaper production. Since it is synthesized from purified protein-free material (dextran), it seems unlikely to give rise to protein-sensitization reactions, and it can be produced to specified chemical and physical characteristics.

MAXWELL

Selvaag, O., and Riiser, S.: Experiences with Regitine (A New Vasodilator Compound) Acta med. scandinav. **146:** 209 (Fasc. 3), 1953.

Regitine is a synthetic preparation which is a derivative of imidazoline and which has a marked adrenolytic and sympathicolytic effect, exerting its action peripherally. The drug was used orally in 25 patients, 10 of whom had manifestations of Raynaud's syndrome. Five patients in this latter category were benefited. Patients with obliterative vascular disease and others with hypertensive encephalopathy were not greatly benefited by this drug. Side effects noted by these patients included a sensation of heat, oppression in the head, dizziness and palpitations. These symptoms, especially the last, were often severe enough to require omitting the drug. The drug resulted in immediate relief in symptoms and cure after four or five days of treatment when given intramuscularly to two patients with periarthritis humeroscapularis.

When injected intra-arterially in normal persons, Regitine produced dilatation of the vessels of the extremity treated and this dilatation was found to last for several hours in some instances. Hyperemia was produced by administration of the drug by this route in a small series of patients with peripheral vascular disorders, and when the obliterative element of the vascular disease was not too far advanced, this was associated with a rise of skin temperature. Hypotension commonly occurs after intra-arterial administration of the drug, and it is advised that patients undergoing such treatment be allowed to lie down for 15 to 30 minutes after the injection. Regitine is said to produce the same effects as Benzazolin (Priscol group) in patients and normal subjects.

ROSENBAUM

Brodwall, E. K.: The Resorption of Theophyllamine (Theophylline Ethylenediamine). Blood Concentrations after Intravenous, Peroral, Rectal and Intramuscular Administration. Acta med. scandinav. **146:** 123 (fasc. 2), 1953.

The blood concentrations of theophylline, achieved by different routes of administration of theophyllamine, were determined by the method of Schack and Waxler. After the intravenous injection of 0.3 Gm. of the drug, a high concentration of 7 μg. per milliliter was found in 15 minutes, with a rapid fall during the next hour. Only negligible amounts of the drug were present in the blood after seven hours. After the oral administration of 0.3 Gm. of theophyllamine, the blood concentration in one hour was approximately 4 μg. per milliliter. This value remained quite constant for four to five hours but became negligible after 10 hours. The drug was given rectally in suppositories containing 0.5 Gm. Absorption was found to be slow with a maximal concentration appearing after four hours and moderate amounts still remaining after 10 hours. When 0.3 Gm. of theophyllamine was given intramuscularly, absorption was fairly rapid but the concentration of theophylline in the blood remained low.

The author concludes that peroral administration should be preferred where treatment is required over a long time, and the intravenous route should be used in acute cases. Rectal or intramuscular administration appears to have no advantage over the oral route.

ROSENBAUM

Ditlefsen, E. L.: Concentrations of Quinidine in Blood Following Oral, Parenteral and Rectal Administration. Acta. med. scandinav. **146:** 81 (fasc. 2), 1953.

Extensive studies of the concentration of quinidine in the blood after various modes of administration are reported. The highest and earliest peaks of concentration of quinidine in the blood were recorded after oral administration on an empty stomach. Although there were individual variations, the peak level after a single oral dose of 0.6 Gm. was 1.0 mg. per liter lower and occurred about one hour later when given after breakfast. A preparation of quinidine hydrochloride dissolved in urea and antipyrine was used intramuscularly in three persons. The peak level was not as high as that after oral administration, but the eight hour residual level was higher by this method. Though

the series studied was small, rectal administration seemed an unsatisfactory method. A technic used in treatment of five patients with auricular fibrillation is described. This consisted of giving 0.3 Gm. quinidine sulfate every four hours for 24 hours, the same dose at three hour intervals for a second 24-hour period, and, finally, the same dose at two-hour intervals for the third 24-hour period. Conversion to normal rhythm was achieved in three of the five patients although the full course was not required in two of them. The highest level achieved by this dosage schedule was 12 mg. per liter. A patient is described who was given 0.2 Gm. of quinidine sulfate at intervals of 10 minutes until a total dose of 1.4 Gm. was given. A maximum blood level of 11.03 mg. per liter was reached in two and one-half hours. A second patient was given 0.1 Gm. of quinidine sulfate at 10-minute intervals for a total dose of 0.8 Gm. The blood level rose to 10.41 mg. in one and one-half hours. It is suggested that this method may be especially useful when rapid effect is desired. So far as prophylactic quinidine treatment is concerned, the fewest fluctuations were observed when the drug was given at evenly spaced intervals throughout the day.

Electrocardiographic changes resulting from quinidine consisted of prolongation of the Q-T interval and flattening of the T waves, which in some cases also became diphasic. The maximum prolongation of the Q-T interval appeared to coincide with the maximum blood quinidine level.

ROSENBAUM

Hejtmancik, M. R., Futch, E. D., and Herrmann, G. R.: Clinical Effects of Khelltron in Angina Pectoris. Texas J. Med. **49:** 679 (Sept.), 1953.

Khelltron, (a combination of 20 mg. crystalline khellin, 40 mg. Sestron monocitrate, and 3 mg. thiamine hydrochloride) was administered to 41 ambulatory patients with angina pectoris. The therapeutic effects were analyzed and compared with symptoms during a preliminary control period, placebo therapy, and, in some instances, treatment with khellin and Peritrate. Khelltron produced definite improvement in 27 of the patients. However, it had to be discontinued in eight of these because of toxic effects. Thus, 19 experienced definite improvement without toxicity. Incidence of side effect appeared about one-half as frequently as with khellin, being noted in less than one-third of the entire series.

BERNSTEIN

Kitto, H. J., and Bohr, David F.: Some Agents which Potentiate the Inotropic Response of the Papillary Muscle to Epinephrine. Am. J. Physiol. **175:** 343 (Dec.), 1953.

The positive inotropic effect of epinephrine upon papillary muscle is potentiated by cysteine, cystine, tyrosine, ascorbic acid and plasma. However, the positive inotropic action of barium chloride is not influenced by cysteine. Benadryl and indol-acetic acid, which are amine-oxidase inhibitors, do not increase the epinephrine response. The suggestion is made by the authors that the potentiating agents in these experiments act by removing trace amounts of heavy metals which catalyze the autoxidation of epinephrine. They neutralize the blocking action of copper on epinephrine.

OPPENHEIMER

Heimdal, A., and Nordenfelt, O.: The Effect of Hydergine on the Electrocardiogram. Cardiologia **23:** 358 (Fasc. 6), 1953.

In 30 subjects with normal hearts and varying degrees of orthostatic alterations of the electrocardiogram, the pulse rate, blood pressure, and electrocardiograms were recorded in recumbent and erect positions before and after intramuscular injection of 0.3 mg. of Hydergine. Comparison with similar experiments with 0.5 mg. of Ergotamin injected intravenously showed that normalization of an anomalous orthostatic electrocardiogram was less complete following Hydergine. This is probably due to the fact that Hydergine reduces the heart rate to a much lesser degree than Ergotamin. Higher doses of Hydergine cannot be used because of its tendency to produce orthostatic collapse.

PICK

Sanderson, G. M., Jr., and Hubbard, R. S.: Qualitative Difference between Levoepinephrine and Levoarterenol. Arch. Surg. **67:** 746 (Nov.), 1953.

The authors studied the effect of levoarterenol and levoepinephrine on arterial, portal venous, and right auricular pressures and on cardiac rate in a series of 24 dogs. Arterial pressure was consistently elevated by arterenol but depressed by epinephrine. The cardiac rate was slowed by arterenol, while epinephrine caused a transient tachycardia.

To account for such differences, the thesis was proposed that Arterenol is a vasoexcitor substance, while epinephrine is a vasoinhibitor substance. Demethylation, at some site in the body, possibly the liver, effects a transformation of epinephrine into Arterenol in response to the need for the maintenance of normal tonus.

ABRAMSON

Moyer, J. H., and Johnson, I.: Intramuscular Veriloid (Aqueous Solution) as a Hypotensive Agent. Am. J. M. Sc. **226:** 477 (Nov.), 1953.

Repeated intramuscular injections of Veriloid were employed in hypertensive patients with a satisfactory reduction of blood pressure to approximately 150/100 in all instances. There were no evidences of arterial insufficiency related to cerebral, coronary or renal circulations associated with the lowering of blood pressure. The average duration of the effect which began within 30 minutes was three

and one-fourth hours. The initial recommended dose was 0.6 mg., increasing in 0.2 mg. increments until a satisfactory blood pressure response was observed. Reproducibility of the hypotensive effect on a given dose was found to be adequate. Side reactions of hiccoughs, salivation, nausea and vomiting occurred in about half the patients. The established intramuscular dose may be administered at approximately six-hour intervals depending on individual requirements. The use of a continuous intravenous dosage to establish the intramuscular dosage requirements was unsatisfactory. The intramuscular administration of Veriloid was considered a practical therapeutic procedure for hypertensive emergencies and for bedfast patients, since it reduces the supine as well as the erect blood pressures.

SHUMAN

Cloetens, W., and De Mey, D.: Particular Evolution of a W-P-W Syndrome. Pharmacologic Effects of Procaine Amide. Acta cardiol. **8:** 632 (Fasc. 6), 1953.

A case of a 47 year old woman is described in whom an intermittent Wolff-Parkinson-White syndrome and ventricular premature systoles appeared in the course of acute rheumatic carditis. Following intravenous injection of 300 or 500 mg. of procaine amide, the ectopic beats transiently disappeared, while at the same time, the Wolff-Parkinson-White beats became persistent. It would, therefore, appear that ectopic impulse formation and the phenomenon of ventricular pre-excitation represent two different mechanisms, and that the Wolff-Parkinson-White syndrome cannot be explained on the basis of ventricular hyperexcitability.

PICK

Van Hees, C. A.: Effect of Procaine Amide on the Syndrome of W-P-W. Acta cardiol. **8:** 639 (Fasc. 6), 1953.

A case is described of a young woman with persistent Wolff-Parkinson-White syndrome and attacks of supraventricular paroxysmal tachycardia. When such an attack was stopped by intravenous injection of procaine amide, the pre-excitation syndrome transiently disappeared. This observation can be explained by either of the two principal theories advanced for the interpretation of the Wolff-Parkinson-White syndrome. Procaine amide could have temporarily interrupted conduction through an anomalous A-V conduction pathway, or suppressed a hyperexcitable ventricular focus.

PICK

Moyer, J. H., Handley, C. A., Seibert, R. A., and Snyder, H. B.: Electrolyte, Water, and Mercury Excretion after Oral Administration of Neohydrin. Arch. Int. Med. **92:** 847 (Dec.), 1953.

Electrolyte, water, and mercury excretion studies have been done after the oral administration of two thiol mercurial and one chloromercurial (Neohydrin) experimental diuretics. The chloromercurial, Neohydrin, appears to be the most effective diuretic as estimated by the increased excretion of sodium and water. The increased effectiveness is probably due to greater absorption from the intestinal tract and consequently greater excretion in the urine. In addition, Neohydrin has more potent diuretic properties.

Approximately 5 to 10 per cent of the amount of diuretic ingested is absorbed and excreted in the urine, as estimated by mercury excretion determinations. The renal thresho d for the production of diuresis appears to be 5 to 8 mg. Hg. Therefore, the diuretic must be ingested in amounts containing 60 to 80 mg. Hg if adequate amounts are to be absorbed and consistently delivered to the renal tubules. Increased sodium excretion has been observed on smaller amounts (40 mg. Hg four tablets) which was not associated with increased water excretion. This phenomenon may deplete stored sodium if the drug is given daily and thus prevent cardiac failure for prolonged periods of time, despite the fact that acute diuresis cannot be demonstrated after this dose of Neohydrin.

BERNSTEIN

Russo, G.: Late Results of Treatment of Pericarditis with Effusion by Pneumopericardium. Cuore e circolaz. **37:** 14, 1953.

Seven cases of pericarditis with effusion are studied. Repeated pneumoparacentesis and causal treatment were done in all cases until clinical and roentgenologic data showed a complete recovery. Streptomycin or penicillin were injected into the pericardium in some cases. Four cases were followed for several years. The introduction of air was found to prevent the formation of adhesions. Thereby, prognosis was greatly improved.

LUISADA

Ohler, E. A., and Sevy, R. W.: Effect of Pressor Amines and Adrenergic Blockade on Adrenal Ascorbic Acid Concentration in Rats. Am. J. Physiol. **175:** 285 (Nov.), 1953.

Paredrine decreases adrenal ascorbic acid in normal rats. However, removal of the hypophysis prevents this effect. Prior administration of Dibenzyline blocks the effects of both epinephrine and Paredrine. It is pointed out that Dibenzyline does not deplete adrenal ascorbic acid when used alone; this differs from Dibenamine. Since ephedrine has no effect on adrenal ascorbic acid, the authors point out that pressor activity and the ability to stimulate the pituitary-adrenal system are probably not related.

OPPENHEIMER

PHYSICAL SIGNS

Talbott, J. H., and Montgomery, W. R., Jr.: Familial Clubbing of Fingers and Toes. Arch. Int. Med. **92:** 697 (Nov.), 1953.

A large family has been observed which is com-

ised of five generations. A majority of the members exhibit clubbing of the fingers, sometimes known as "hippocratic nails," without evidence of systemic disease. The family pedigree suggests that the trait is hereditary and that it behaves in the manner of a simple Mendelian dominant without sex linkage or influence. These observations accentuate the fact that clubbing need not necessarily be a diagnostic sign of systemic disease, nor is it in this form a threat to a long and comfortable life.

BERNSTEIN

RHEUMATIC FEVER

Cajander, B.: Observations on a Cortisone-Like Effect on Injection of Desoxycorticosterone acetate (DOCA) in Combination with Ascorbic Acid in Rheumatic Diseases. Acta med. scandinav. **147:** 53 (Fasc. 1), 1953.

The author reports upon the response of 60 patients to treatment with mg. desoxycorticosterone acetate intramuscularly and 10 ml. of 10 per cent ascorbic acid solution intravenously, twice daily for 10 days. Some patients received two or three such courses of treatment. The series consisted of 45 patients with rheumatoid arthritis, four cases of rheumatic fever, seven cases of spondylitis ankylopoietica, one case of Reiter's syndrome and three cases of disseminated lupus erythematosus. Of the patients with rheumatoid arthritis, slightly more than two-thirds were favorably influenced, and the majority of them showed distinct objective improvement.

It was concluded that in some cases of rheumatoid disease there was definitive subjective and objective improvement, whereas in others, no such effect could be demonstrated, and in some there was actual deterioration. The cause of these variations in response is not clear. It is assumed that in certain cases desoxycorticosterone acetate and ascorbic acid produce a cortisone-like effect by adjusting the hormonal balance.

ROSENBAUM

ROENTGENOLOGY

Zinsser, H. F. Jr., and Johnson, J.: The Use of Angiocardiography in the Selection of Patients for Mitral Valvular Surgery. Ann. Int. Med. **39:** 1200 (Dec.), 1953.

Based on an angiocardiographic study of 150 patients with mitral disease, a characteristic angiocardiographic pattern could be demonstrated in those patients who were found at operation to have significant mitral stenosis with little or no regurgitant jet. The value of the study is somewhat limited by the fact that it provides very little additional information in patients with typical clinical findings of "pure" mitral stenosis. The procedure's greatest value is due to its dependability in establishing the diagnosis of mitral valvular obstruction, when the clinical findings make such a diagnosis difficult or uncertain; for example, in five patients, mitral stenosis was shown to be present when a diastolic murmur could not be heard and in 72 others the angiocardiogram was considered characteristic of mitral stenosis even though the predominant murmur at the apex was systolic in time.

WENDKOS

Nazzi, V.: The Clinical Diagnosis of Thrombosis of the Left Auricular Appendage. Cuore e circolaz. **37:** 193, 1953.

Two cases of mitral valvular disease are presented with recording of the electrocardiogram, the roentgenkymogram, and the jugular and esophageal tracings. While the various tracings showed good contractions of both atria (sinus rhythm in one case, atrial flutter in the other), the roentgenkymogram showed immobility of that segment on the left border which is between pulmonary arch and left ventricle. This finding was interpreted as suggestive of thrombosis of the left auricular appendage. The diagnosis was confirmed in one case by autopsy. The importance of the diagnosis during life is apparent because resection of the appendage, or treatment with anticoagulants, may prevent future embolisms.

LUISADA

Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I., and Rusoff, J. H.: Determination of C-reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever. Am. J. Med. **15:** 645 (Nov.), 1953.

After studying the C-reactive protein changes in 62 patients with rheumatic fever, the authors conclude that the presence of C-reactive protein in the blood of a rheumatic patient is a sensitive and reliable indicator of rheumatic activity if other unrelated pathologic processes can be excluded. This protein, not normally present in the blood of humans, appears in response to a variety of inflammatory stimuli and may be identified by its capacity to form a precipitate with the somatic C-polysaccharide of the pneumococcus.

Certain isolated rheumatic manifestations, such as chorea, erythema marginatum, subcutaneous nodules and Aschoff bodies in the auricular myocardium, may be present without causing the appearance of C-reactive protein in the patient's blood. The disappearance of C-reactive protein from the blood is a good prognostic sign for the termination of a rheumatic attack but does not preclude the possibility of a future polycyclic recurrence. Persistence of C-reactive protein in the blood during treatment with antirheumatic agents indicates inadequate suppression of the inflammatory process.

HARRIS

Brown, E. M., Jr., Frain, J. B., Udell, L., and Hollander, J. L.: Locally Administered Hydrocortisone in the Rheumatic Diseases. A Summary of Its Use in 547 Patients. Am. J. Med. **15:** 656 (Nov.), 1953.

After injecting hydrocortisone into inflamed

and one-fourth hours. The initial recommended dose was 0.6 mg., increasing in 0.2 mg. increments until a satisfactory blood pressure response was observed. Reproducibility of the hypotensive effect on a given dose was found to be adequate. Side reactions of hiccoughs, salivation, nausea and vomiting occurred in about half the patients. The established intramuscular dose may be administered at approximately six-hour intervals depending on individual requirements. The use of a continuous intravenous dosage to establish the intramuscular dosage requirements was unsatisfactory. The intramuscular administration of Veriloid was considered a practical therapeutic procedure for hypertensive emergencies and for bedfast patients, since it reduces the supine as well as the erect blood pressures.

SHUMAN

Cloetens, ..., and De Mey, D.: Particular Evolution of a W-P-W Syndrome. Pharmacologic Effects of Procaine Amide. Acta cardiol. **8:** 632 (Fasc. 6), 1953.

A case of a 47 year old woman is described in whom an intermittent Wolff-Parkinson-White syndrome and ventricular premature systoles appeared in the course of acute rheumatic carditis. Following intravenous injection of 300 or 500 mg. of procaine amide, the ectopic beats transiently disappeared, while at the same time, the Wolff-Parkinson-White beats became persistent. It would, therefore, appear that ectopic impulse formation and the phenomenon of ventricular pre-excitation represent two different mechanisms, and that the Wolff-Parkinson-White syndrome cannot be explained on the basis of ventricular hyperexcitability.

PICK

Van Hees, C. A.: Effect of Procaine Amide on the Syndrome of W-P-W. Acta cardiol. **8:** 639 (Fasc. 6), 1953.

A case is described of a young woman with persistent Wolff-Parkinson-White syndrome and attacks of supraventricular paroxysmal tachycardia. When such an attack was stopped by intravenous injection of procaine amide, the pre-excitation syndrome transiently disappeared. This observation can be explained by either of the two principal theories advanced for the interpretation of the Wolff-Parkinson-White syndrome. Procaine amide could have temporarily interrupted conduction through an anomalous A-V conduction pathway, or suppressed a hyperexcitable ventricular focus.

PICK

Moyer, J. H., Handley, C. A., Seibert, R. A., and Snyder, H. B.: Electrolyte, Water, and Mercury Excretion after Oral Administration of Neohydrin. Arch. Int. Med. **92:** 847 (Dec.), 1953.

Electrolyte, water, and mercury excretion studies have been done after the oral administration of two thiol mercurial and one chloromercurial (Neohydrin) experimental diuretics. The chloromercurial, Neohydrin, appears to be the most effective diuretic as estimated by the increased excretion of sodium and water. The increased effectiveness is probably due to greater absorption from the intestinal tract and consequently greater excretion in the urine. In addition, Neohydrin has more potent diuretic properties.

Approximately 5 to 10 per cent of the amount of diuretic ingested is absorbed and excreted in the urine, as estimated by mercury excretion determinations. The renal threshold for the production of diuresis appears to be 5 to 8 mg. Hg. Therefore, the diuretic must be ingested in amounts containing 60 to 80 mg. Hg if adequate amounts are to be absorbed and consistently delivered to the renal tubules. Increased sodium excretion has been observed on smaller amounts (40 mg. Hg four tablets), which was not associated with increased water excretion. This phenomenon may deplete stored sodium if the drug is given daily and thus prevent cardiac failure for prolonged periods of time, despite the fact that acute diuresis cannot be demonstrated after this dose of Neohydrin.

BERNSTEIN

Russo, G.: Late Results of Treatment of Pericarditis with Effusion by Pneumopericardium. Cuore e circolaz. **37:** 14, 1953.

Seven cases of pericarditis with effusion are studied. Repeated pneumoparacentesis and causal treatment were done in all cases until clinical and roentgenologic data showed a complete recovery. Streptomycin or penicillin were injected into the pericardium in some cases. Four cases were followed for several years. The introduction of air was found to prevent the formation of adhesions. Thereby, prognosis was greatly improved.

LUISADA

Ohler, E. A., and Sevy, R. W.: Effect of Pressor Amines and Adrenergic Blockade on Adrenal Ascorbic Acid Concentration in Rats. Am. J. Physiol. **175:** 285 (Nov.), 1953.

Paredrine decreases adrenal ascorbic acid in normal rats. However, removal of the hypophysis prevents this effect. Prior administration of Dibenzyline blocks the effects of both epinephrine and Paredrine. It is pointed out that Dibenzyline does not deplete adrenal ascorbic acid when used alone; this differs from Dibenamine. Since ephedrine has no effect on adrenal ascorbic acid, the authors point out that pressor activity and the ability to stimulate the pituitary-adrenal system are probably not related.

OPPENHEIMER

PHYSICAL SIGNS

Talbott, J. H., and Montgomery, W. R., Jr.: Familial Clubbing of Fingers and Toes. Arch. Int. Med. **92:** 697 (Nov.), 1953.

A large family has been observed which is com-

ised of five generations. A majority of the members exhibit clubbing of the fingers, sometimes known as "Hippocratic nails," without evidence of systemic disease. The family pedigree suggests that the trait is hereditary and that it behaves in the manner of a simple Mendelian dominant without sex linkage or influence. These observations accentuate the fact that clubbing need not necessarily be a diagnostic sign of systemic disease, nor is it in this form a threat to a long and comfortable life.

BERNSTEIN

RHEUMATIC FEVER

Cajander, B.: Observations on a Cortisone-Like Effect on Injection of Desoxycorticosterone acetate (DOCA) in Combination with Ascorbic Acid in Rheumatic Diseases. Acta med. scandinav. **147:** 53 (Fasc. 1), 1953.

The author reports upon the response of 60 patients to treatment with mg. desoxycorticosterone acetate intramuscularly and 10 ml. of 10 per cent ascorbic acid solution intravenously, twice daily for 10 days. Some patients received two or three such courses of treatment. The series consisted of 45 patients with rheumatoid arthritis, four cases of rheumatic fever, seven cases of spondylitis ankylopoietica, one case of Reiter's syndrome and three cases of disseminated lupus erythematosus. Of the patients with rheumatoid arthritis, slightly more than two-thirds were favorably influenced, and the majority of them showed distinct objective improvement.

It was concluded that in some cases of rheumatoid disease there was definitive subjective and objective improvement, whereas in others, no such effect could be demonstrated, and in some there was actual deterioration. The cause of these variations in response is not clear. It is assumed that in certain cases desoxycorticosterone acetate and ascorbic acid produce a cortisone-like effect by adjusting the hormonal balance.

ROSENBAUM

ROENTGENOLOGY

Zinsser, H. F. Jr., and Johnson, J.: The Use of Angiocardiography in the Selection of Patients for Mitral Valvular Surgery. Ann. Int. Med. **39:** 1200 (Dec.), 1953.

Based on an angiocardiographic study of 150 patients with mitral disease, a characteristic angiocardiographic pattern could be demonstrated in those patients who were found at operation to have significant mitral stenosis with little or no regurgitant jet. The value of the study is somewhat limited by the fact that it provides very little additional information in patients with typical clinical findings of "pure" mitral stenosis. The procedure's greatest value is due to its dependability in establishing the diagnosis of mitral valvular obstruction, when the clinical findings make such a diagnosis difficult or uncertain; for example, in five patients, mitral stenosis was shown to be present when a diastolic murmur could not be heard and in 72 others the angiocardiogram was considered characteristic of mitral stenosis even though the predominant murmur at the apex was systolic in time.

WENDKOS

Nazzi, V.: The Clinical Diagnosis of Thrombosis of the Left Auricular Appendage. Cuore e circolaz. **37:** 193, 1953.

Two cases of mitral valvular disease are presented with recording of the electrocardiogram, the roentgenkymogram, and the jugular and esophageal tracings. While the various tracings showed good contractions of both atria (sinus rhythm in one case, atrial flutter in the other), the roentgenkymogram showed immobility of that segment on the left border which is between pulmonary arch and left ventricle. This finding was interpreted as suggestive of thrombosis of the left auricular appendage. The diagnosis was confirmed in one case by autopsy. The importance of the diagnosis during life is apparent because resection of the appendage, or treatment with anticoagulants, may prevent future embolisms.

LUISADA

Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I., and Rusoff, J. H.: Determination of C-reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever. Am. J. Med. **15:** 645 (Nov.), 1953.

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HARRIS

Brown, E. M., Jr., Frain, J. B., Udell, L., and Hollander, J. L.: Locally Administered Hydrocortisone in the Rheumatic Diseases. A Summary of Its Use in 547 Patients. Am. J. Med. **15:** 656 (Nov.), 1953.

After injecting hydrocortisone into inflamed

joints or other noninfectious locally diseased tissues of 547 patients with various types of rheumatic disease over an 18-month period, the authors found improvement in 85 per cent of the patients treated and no appreciable therapeutic benefit in 9 per cent. Intra-articular hydrocortisone is a useful adjunct to the usual methods of treatment for rheumatoid arthritis, osteoarthritis, gout, bursitis, and other localized rheumatic disorders. Adverse reactions to this local therapy are few and transient. Contraindications to the use of hydrocortisone locally are: (1) the presence of proven or suspected infection in or near the joint (local instillation of hydrocortisone into or through such diseased tissues may spread the infection), and (2) proven or suspected hypersensitivity to either hydrocortisone or the constituents of the suspending vehicle.

HARRIS

Wells, B. B., and Ross, W. S.: Clinical Pathology of Systemic Lupus Erythematosus. Texas J. Med. **49:** 673 (Sept.), 1953.

Clinical laboratory findings in 47 patients with systemic lupus erythematosus are reported and discussed. The expected leukopenia and hyperglobulinemia were not observed in a large proportion of these cases. Anemia, increased sedimentation rate, and abnormal urinalysis were among the most consistent findings recorded. No test presently available has specific diagnostic value except the demonstration of L.E. cells in bone marrow or peripheral blood, or the L.E. factor in the patient's serum. The L.E. phenomenon may be absent during chronic phases of systemic lupus erythematosus and during spontaneous or induced remission of the disease.

BERNSTEIN

SURGERY

Andrus, E. C., Blalock, A., and Milnor, W. R.: Surgical Treatment of Mitral Stenosis. Arch. Surg. **67:** 790 (Dec.), 1953.

The preoperative and postoperative observations of 75 patients, ranging in age from 20 to 49 years and including 17 men and 58 women, are reported. All survivors have been followed at least six months after operation. Surgical relief of mitral obstruction, now an established procedure, brought considerable and sometimes dramatic improvement to nearly three-fourths of this group of 75 patients, selected because of genuine and progressive circulatory disability. Improvement has persisted in most of the patients followed three years or more. There were two failures in this group and nine deaths. Four patients died of embolism, four of progressive cardiac failure, and one of staphylococcus pericarditis.

The two most devastating complications are embolism at operation and reactivation of rheumatic carditis. The former is a surgical problem. The latter calls for the most thorough application of the only known methods of preventing rheumatic fever; prophylaxis against streptococcus infections of the respiratory tract with sulfadiazine or penicillin or, failing this, the prompt initiation of antibiotic therapy at the onset of the respiratory infection.

DENNISON

Glenn, F., Harrison, C. S., and Steinberg, I.: Pulmonary Arteriovenous Fistula Occurring in Siblings. Ann. Surg. **138:** 886 (Dec.), 1953.

Two sisters are presented who had pulmonary arteriovenous fistulas of the lungs and were successfully operated on. Diagnosis was established from angiocardiograms. The authors point out that the classic triad of cyanosis, pulmonary osteoarthropathy, and polycythemia may not be present. In addition, the classic bruit and the systolic murmur or a machinery-like murmur may only be present in large lesions. Close relationship between pulmonary arteriovenous fistula and the Rendu-Osler-Weber type of congenital telangiectasis is discussed.

The authors strongly believe that the treatment of choice is excision as these lesions tend to progress, often with alarming rapidity. In addition, cases of brain abscess which developed in association with pulmonary arteriovenous aneurysms have been reported. Finally, fatal hemoptysis has also been described. Because of these serious complications, prophylactic surgery to eradicate these lesions seems wise.

DENNISON

Collins, H. A., Stahlman, M., and Scott, H. W., Jr.: The Occurrence of Subcutaneous Fat Necrosis in an Infant Following Induced Hypothermia Used as an Adjuvant in Cardiac Surgery. Ann. Surg. **138:** 880 (Dec.), 1953.

It is felt that the rather unusual complication which developed after induced hypothermia in its initial clinical use in the authors' hands is of sufficient importance to warrant reporting. This is also the first instance of subcutaneous fat necrosis which has resulted from the clinical application of general hypothermia. The infant developed this complication following an end-to-side anastomosis between the left subclavian and left pulmonary arteries for relief of the tetralogy of Fallot.

The authors point out other instances of subcutaneous fat necrosis in children following exposure to cold and indicate that it is not a rare occurrence. The susceptibility to this phenomenon in infants may be related to the difference in the composition of fat of the infant and the adult. Oleic acid is an unsaturated fatty acid and has a much lower melting point than either palmitic or stearic acids. Apparently a very small change in the relative proportions of these acids results in a rather marked alteration of the melting point of the neutral fat. It is thus postulated that a very slight diminution in

temperature can cause solidification of the infant's fat, with subsequent necrosis and inflammatory changes. The authors are anxious that their report not be construed as a condemnation of controlled hypothermia for cardiovascular surgery.

DENNISON

Dodrill, F. D., Hill, E., Gerisch, R. A., and Johnson, A.: Pulmonary Valvuloplasty Under Direct Vision Using the Mechanical Heart for a Complete By-Pass of the Right Heart in a Patient with Congenital Pulmonary Stenosis. J. Thoracic Surg. **26:** 584 (Dec.), 1953.

The authors point out that congenital pulmonary stenosis means the stenosis of the pulmonary valve or infundibulum without overriding of the aorta. The majority of patients with obstruction to the outflow of the right ventricle have defects in either the interatrial or interventricular septum, although there are some patients without other defects aside from the stenosis itself.

The authors point out that when the valve is cut with the valvulotome, through the lined transventricular technic, there is no assurance that the incision may not heal, producing the original obstruction. Therefore, with this thought in mind, the mechanical heart has been applied to a patient with congenital pulmonary stenosis. The right heart was completely by-passed. The main pulmonary artery was clamped off for 25 minutes while the left heart and lungs continued to perform their function. The pulmonary valve was exposed and enlarged under direct vision. The lung flaps of valve tissue protruding into the pulmonary artery were excised. The blood flow through the mechanical heart was 4.5 liters per minute.

The procedure was successful and the patient has been vastly improved. This is, to the authors' knowledge, the first instance of a complete by-pass of the right heart in a patient. Obviously, there must not be a defect of the cardiac septa with such a procedure.

DENNISON

Bahnson, H. T.: Considerations in the Excision of Aortic Aneurysms. Ann. Surg. **138:** 377 (Sept.), 1953.

The author reported the results in 17 patients of excision of aneurysms in various regions of the aorta. In some instances homografts were utilized. The operation was successful in 12 cases.

It was the author's belief that such a procedure, by preserving the continuity of the aorta, has much to recommend it. When feasible, it allows the removal of the lesion and the restoration of the vessel to as nearly a normal size as possible.

ABRAMSON

VASCULAR DISEASE

Megibow, R. S., Megibow, S. J., Pollack, H., Bookman, J. J., and Osserman, K.: The Mechanism of Accelerated Peripheral Vascular Sclerosis in Diabetes Mellitus. Am. J. Med. **15:** 322 (Sept.), 1953.

The authors evaluated the peripheral circulation of 47 diabetic patients below the age of 45 years with a microplethysmographic method. Although standard diagnostic technics failed to demonstrate impairment of the peripheral circulation in each subject, with this new technic 22 of the 47 patients, following the administration of nitroglycerine, did show significant differences in blood flow and volume pulse amplitude in one great toe as compared with the contralateral toe. After ganglionic blockade by tetraethylammonium, 15 of these 22 patients continued to manifest significant reductions in flow and volume in one of the two halluxes. The authors consider these findings to imply the presence of occlusive peripheral vascular disease localized to the digital bed in view of the normal oscillometric index. It is suggested that the lesions in the digital bed are analogous to the vascular lesions of diabetic retinitis and intercapillary glomerulosclerosis, and constitute an integral manifestation, not a secondary complication of diabetes mellitus. The increased proximal resistance which will follow upon the development of a more occlusive angiopathy is considered to account, at least in part, for the increased incidence and accelerated development of clinical arteriosclerosis in diabetes. These alterations in the minute digital blood vessels appear to represent a vascular change distinct from the usual type of peripheral arteriosclerosis.

HARRIS

Wisham, L. H., Abramson, A. S., and Ebel, A.: Value of Exercise in Peripheral Arterial Disease. J.A.M.A. **153:** 10 (Sept. 5), 1953.

The authors studied the vasodilating effect of exercise in normal subjects and in patients with arterial vascular disorders by using the measurement of the clearance of radiosodium (Na^{24}) from tissues. They found that passive postural exercises did not increase muscle blood flow significantly, while active exercise was quite effective in this regard.

ABRAMSON

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ASSOCIATION GRANTS-IN-AID

Applications for Research Grants-in-Aid for the 1955–56 fiscal year *must be received on or before Dec. 1, 1954.* Grants are made to nonprofit institutions in direct support of a particular investigator, for a specific program of research under his direction. Grants are awarded in support of research in the cardiovascular field or basic sciences related to it in amounts up to $10,000 per annum for periods of one or more years. Information and application forms may be obtained from the Association's Medical Director. The deadline for Fellowships and Established Investigatorships expired Sept. 15, 1954.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

Discussions on nerve transmission and muscle metabolism will be featured on the scientific program to be presented at the Annual Meeting of the Council for High Blood Pressure Research of the American Heart Association in Cleveland on Friday and Saturday, October 22 and 23, at the Hotel Cleveland.

Participants in the opening Friday morning session on "Nerve Transmission and Related Problems" will include Amedeo Marrazzi, M.D., Army Chemical Center, Maryland, and Steven W. Kuffler, M.D., Johns Hopkins Medical School, Baltimore.

Both morning and afternoon sessions of the scientific program on Saturday will be devoted to the subject of "Muscle Metabolism and Related Problems." Wilfried F. H. M. Mommaerts, Ph.D., Western Reserve University School of Medicine, Cleveland, and Albert Szent-Györgyi, M.D., Institute of Muscle Research, Woods Hole, Mass., will speak at the morning session. Participants in the afternoon panel discussion will include Albert Szent-Györgyi, M.D., Wilfried F. H. M. Mommaerts, Ph.D., and Victor Lorber, M.D., University of Minnesota, Minneapolis.

A session for lay members on Friday afternoon, considering "Problems of Retirement," will be chaired by Irving S. Wright, M.D., New York Hospital-Cornell University Medical Center, New York. Participants will include Louis Karnosh, M.D., psychiatrist; A. Carlton Ernstene, M.D., Cleveland Clinic; Edward M. Kline, M.D., medical consultant, Lamp Division, General Electric Co.; Frank Joseph, attorney; and John Sherwin, industrialist, all of Cleveland.

The guest speaker at the Council's Annual Dinner on Friday evening will be Percival Bailey, M.D., University of Illinois College of Medicine, Chicago.

ABSTRACTS OF SECOND WORLD CONGRESS

The printed program of the Second World Congress of Cardiology and the 27th Scientific Sessions of the American Heart Association which was held in Washington, D. C. September 12–17 is now available at $3.00 a copy. The 500-page volume contains abstracts of papers presented at the formal scientific sessions. These are printed in English and with translations in Interlingua, a new international language, and in some cases in their original language. Interlingua is a combination of all the common elements of Western languages now in use and is almost immediately familiar to anyone who has any knowledge of these tongues. Copies of the program may be obtained from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

REPORT OF COMMITTEE ON ANTICOAGULANTS

A report of the findings of a Committee on Anticoagulants established by the American Heart Association in 1946 to conduct an exten-

sive study of these drugs has just been issued. The 680-page volume, entitled "Myocardial Infarction: A Study of 1031 Cases; Its Clinical Manifestations and Treatment," has been published by Grune & Stratton, Inc., New York ($8.50). The authors are Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D.

The result of seven years of investigation, the report is based on work done in 16 widely scattered cooperating hospitals. The volume provides a full analysis of the entire series of cases, and includes 480 tables and charts. Dr. Wright, Professor of Clinical Medicine at Cornell University College of Medicine, New York, was Chairman of the Committee. Dr. Marple, presently Medical Director of the American Heart Association, acted as Coordinator of the study. Dr. Beck directed the statistical analysis.

"ATLAS OF CONGENITAL CARDIAC DISEASE" REPRINTED

In response to numerous requests from physicians, students, scientific workers and libraries throughout the world, the American Heart Association has reprinted the "Atlas of Congenital Cardiac Disease," by Maude F. Abbott, M.D. This classic monograph, a critical analysis of 1000 cases of congenital cardiac anomalies, was first published by the Association in 1936. Long since out of print, it has now been reprinted in a limited edition of 1500 numbered copies exactly as it appeared originally.

The work of Dr. Maude Abbott, who died in 1940, served to bridge the gap between the previous unsystematic and largely descriptive knowledge of congenital cardiac defects and the present era of precise diagnosis and dramatic surgery.

The monograph was published largely at the suggestion of and with the encouragement of William W. Francis, M.D., of the Osler Library, McGill University, Montreal, and with the permission of the executors of Dr. Abbott's estate.

The volume, which was printed by Peter F. Mallon, Inc., Long Island City, is available at a cost of $5.00. Copies may be obtained from the National Office of the American Heart Association or through affiliated heart associations and medical booksellers.

ANATOMIC CARDIAC STAMPS

Sets of anatomic cardiac rubber stamps are now available at cost to interested physicians to assist them in keeping records of heart patients. The rubber stamps were devised from diagrams in the book "Congenital Malformations of the Heart," by Helen Taussig, M.D., published by the Harvard University Press for the Commonwealth Fund.

Stamp imprints show outlines of the heart and chest which enable physicians to record fluoroscopic findings of disease conditions or abnormal changes in the heart shadow. They are available in three categories: (1) *Infant;* small size, $1\frac{1}{2} \times 1\frac{1}{4}$ inches; large size, $2 \times 1\frac{3}{4}$ inches. (2) *Child*; small size, $1\frac{1}{2} \times 1\frac{1}{4}$ inches, large size, $2 \times 1\frac{3}{4}$ inches. (3) *Adult*; one size only, $2 \times 1\frac{3}{4}$ inches. Three views are available in each size, anterior posterior, left anterior oblique and right anterior oblique.

The stamps are distributed nationally by the Stamford Heart Association, 190 W. Broad Street, Stamford, Connecticut, at the cost price of $3.00 for each category (three stamps), postpaid.

WASHINGTON SYMPOSIUM

The Sixth Annual Symposium on Heart Disease, sponsored by the Washington State Heart Association and the Washington State Department of Health, will be held at the University of Washington, Seattle, Friday and Saturday, November 5 and 6, 1954.

The theme of the Symposium will be "Application of Cardiopulmonary Reflexes to Clinical Practice." Eugene Stead, M.D., Durham, N. C.; Richard Ebert, M.D., Chicago, Ill.; and Richard Lyons, M.D., Syracuse, N. Y., will participate. This Symposium is the equivalent of nine hours of formal postgraduate training for members of the Academy of General Practice.

Further details may be obtained by writing Merritt H. Stiles, M.D., President, Washington State Heart Association, 5100 Arcade Building, Seattle 1, Wash.

MEETINGS CALENDAR

Oct. 11–15: American Public Health Association; Buffalo, N. Y.; R. M. Atwater, Secretary, 1790 Broadway, New York 19.

Oct. 17–20: Association of American Medical Colleges; French Lick, Ind.; Dean F. Smiley, M.D., Secretary, 185 North Wabash Avenue, Chicago, Ill.

Oct. 22–23: Annual Meeting and Scientific Program, Council for High Blood Pressure Research, American Heart Association, Cleveland; Irving S. Wright, M.D., Chairman, Program Committee, % American Heart Association, 44 East 23rd Street, New York 10.

Oct. 24–27: National Rehabilitation Association; Annual Meeting, Baltimore, Md., Executive Director, E. B. Whitten, 1025 Vermont Avenue, N. W., Washington, D. C.

Oct. 25–30: College of American Pathologists, Washington, D. C., Arthur H. Dearing, Secretary, 203 North Wabash Avenue, Chicago, Ill.

Oct. 26–29: American Dietetic Association, Annual Meeting; Philadelphia; Mrs. Thelma Pollen, Public Relations Director, 620 North Michigan Avenue, Chicago, 11, Ill.

Oct. 27–29: Henry Ford Hospital and Edsel B. Ford Institute for Medical Research; International Symposium on the Hypophyseal Growth Hormone, Its Nature and Actions; Detroit; Richmond W. Smith, Program Committee, Henry Ford Hospital, Detroit 2, Mich.

Oct. 31–Nov. 1: American Society for the Study of Arteriosclerosis, Annual Meeting; Sheraton Hotel, Chicago; O. J. Pollak, M.D., Secretary, P. O. Box 228, Dover, Del.

Nov. 3–5: National Society for Crippled Children and Adults, Annual Convention; Hotel Statler, Boston; Lawrence J. Linck, Executive Director, 11 South La Salle Street, Chicago 3.

Nov. 4–6: National Committee on Aging; New York, N. Y., Mrs. Geneva Mathiasen, Secretary, National Social Welfare Assembly, 345 East 46 St., New York 17.

Nov. 29–Dec. 2: American Medical Association, Clinical Meeting; Miami; George F. Lull, M.D., Secretary, 535 North Dearborn St., Chicago 10, Ill.

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